CARDIOVASCULAR DISEASES, RISK FACTORS AND COGNITIVE DECLINE IN THE GENERAL POPULATION

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DECLARATION

I, Snorri Björn Rafnsson, declare that this thesis is my own composition.

I administered cognitive function tests to the Edinburgh Artery Study participants in 2002/3 in collaboration with others. I have prepared and analysed the data pertaining to those tests. The Edinburgh Artery Study was already in progress when my project commenced. Therefore, the earlier data, employed widely for the present purposes, were collected through the effort of other colleagues.

This thesis has not been submitted for any other degree or professional qualification.

Signed..

Date.......18/05/07.......

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ABSTRACT

Cognitive function constitutes a critical dimension of the health status of elderly individuals. Age-associated decline in cognitive function may partly be attributed to the negative effects of systemic medical diseases and related factors, including cardiovascular diseases (CVDs) and vascular risk factors. Cognitive decline has been an understudied outcome in cardiovascular epidemiological research. Few reports have comprehensively examined cognitive function in relation to clinical manifestations of systemic atherosclerotic disease in different arterial beds. Inconsistent findings are common in the literature and these are likely to reflect the vast differences between studies regarding the choice of population under study, the methods applied for measuring and defining CVD, the types and timing of administration of protocols used for assessing cognitive function, and the paths taken in the analysis of data.

The principal aim of the present study was to examine the longitudinal change in cognitive test performance in relation to major clinical CVDs and vascular risk factors in a population-based sample of older people. The administration of a battery of neuropsychological tests on two separate occasions facilitated the study of actual change in both general cognition and across different cognitive abilities according to an objectively-determined CVD status. A valid estimation of peak prior cognitive ability allowed the exploration of the impact of CVD and risk factors on the imputed decline from best-ever level of cognitive function to that measured in old age.

The analysis is based on a cohort of 809 men and 783 women aged 55-74 years which in 1987/8 was randomly selected from the general population of Edinburgh. A comprehensive assessment of the prevalence of major CVDs and vascular risk factors was held at baseline and during two follow-up examinations. Since baseline, the study sample has been followed up to determine the incidence of angina pectoris, peripheral arterial disease (PAD), myocardial infarction (MI), and stroke. Cognitive testing was first held in 1998/9 when the mean age of the surviving cohort (n=1209) was 73.1 years (SD=5.0) and subsequently about four years later

using the same test protocol. The present investigation is based on the 452 study participants who attended follow-up cognitive testing in 2002/3.

Both general cognition, as indexed by a general cognitive factor representing the variance common to all the cognitive tests used, and most individual cognitive measures were negatively affected in participants with CVD but no evidence of stroke relative to non-vascular controls. Of the specific CVD manifestations, stroke was significantly associated with a steeper four-year decline in both general cognitive function and verbal memory. When decline was estimated from peak, prior cognitive level, stroke was related to a greater decline in both general cognition and verbal fluency. In the absence of stroke, MI was associated with an accelerated four-year decline in non-verbal reasoning ability but the presence of angina was not related to cognitive decline in this study. Symptomatic PAD also independently predicted faster decline in both general cognition and verbal memory over the four-year follow-up. Several potentially modifiable vascular risk factors, including education, body mass index, smoking, diastolic blood pressure, inflammatory markers and blood viscosity were also related to decline in general and specific cognitive abilities, independently of age, sex, prior cognitive ability and vascular disease. The associations with decline in specific cognitive measures principally resulted from the impact of atherosclerotic disease and risk factors on general cognitive ability rather than the individual functions per se.

The findings from the present study further add to those of previous investigations demonstrating a relationship between CVDs, vascular risk factors, and cognitive decline in older people. Specifically, they reveal that, even in the absence of overt stroke, clinical CVDs are associated with a greater cognitive decline in the elderly, independently of potential confounding by a wide range of vascular risk factors. Also, the relationships between several vascular risk factors and cognitive decline proved to be independent of overt co-existing vascular pathology. Based on these findings, further study is needed to determine the combined effects of CVDs and multiple risk factors on cognitive outcomes in samples of older people. In addition, what the likely pathological mechanisms are underlying cognitive decline associated with atherosclerotic disease and vascular risk factors needs to be addressed in future studies. From a perspective of preventing or delaying vascular-based cognitive decline and impairment, more research is required to assess the effectiveness of both individual and population-based strategies targeting vascular disease and risk factors in older age groups. Finally, further investigation is needed to address the potential impact of subtle cognitive deficits on indicators of the quality of life and the capability of self-maintenance of elderly vascular patients, on adherence to medical treatment and rehabilitation, and further cognitive decrements and survival.

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LIST OF ABBREVIATIONS

BMI	body mass index
CHD	coronary heart disease
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
DST	Digit Symbol-Coding Test
EAS	Edinburgh Artery Study
ECG	electrocardiograph
GCF	general cognitive factor
HADS	Hospital Anxiety and Depression Scale
HDL	high-density lipoprotein
ICAM-1	intercellular adhesion molecule 1
ICD	International Classification of Diseases
IL-6	interleukin-6
IQR	interquartile range
LDL	low-density lipoprotein
LMT	Logical Memory Test
MI	myocardial infarction
MMSE	Mini-Mental State Examination
NART	National Adult Reading Test
PAD	peripheral arterial disease
RPM	Raven's Standard Progressive Matrices
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
VCAM-1	vascular cell adhesion molecule 1
VFT	Verbal Fluency Test

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CHAPTER ONE

General Background to Atherosclerotic Diseases, Risk factors and Neurocognitive Function

1.1. INTRODUCTION

With falling fertility rates and an increase in average life expectancy, which is largely driven by a shift in mortality into older age, many societies worldwide are currently facing significant changes in their demographic structure. A major consequence of this process is the ageing of populations, characterised by both an absolute and relative increase in older people (OECD, 2005). For example, at the end of last century in the United States, the proportion of people 65 years and older was approximately 13% compared to around 4% in 1900 (Fried, 2000). By 2030, the proportion of those aged over 65 years is projected to increase to more than 20%. Similar future population trends have also been forecast for many European countries, including the United Kingdom.

In concert with the ongoing demographic ageing, the need to realise better the spectrum of health and disease of ageing populations, the underlying contributing factors, and any opportunities for both preventive strategies and effective interventions, has taken its place at the forefront of epidemiological research and public health (Fried, 2000). Concomitantly, there are concerns about how traditional systems will respond to the future needs of older people for long-term health and social care. In this context, intact cognitive function, which relates to an individual's ability to process information, emerges as a critical dimension of the health status of elderly people (Fried, 2000; Waldstein and Elias, 2003). Whereas subtle cognitive dysfunction may prevent an individual from performing at the highest possible level of ability, cognitive impairment, which manifests itself in mild to severe changes across different cognitive functions, constitutes a major determinant of long-term institutionalisation and dependency in old age (Melzer et al., 1997; Waldstein and Elias, 2003).

In addition to placing a greater burden on formal and informal pathways of care, impaired cognition is further associated with a significantly reduced quality of life and survival (Neale et al., 2002). The large projected increase in the prevalence of cognitive impairment during the 21st century underscores the importance of the continuing study of aetiological factors, which if appropriately identified and controlled, may pave the way for delaying the onset and reducing the burden of cognitive decline (Purandare et al., 2005; Román, 2003).

A crucial issue in the study of the health status of elderly people is the high prevalence of chronic diseases and associated risk factors, accompanied by an elevated risk of mortality, morbidity, and disability (Fried, 2000). Atherosclerotic CVDs currently constitute a major cause of mortality and morbidity in elderly people in many societies (Román, 2003). Despite a significant decline in mortality from coronary heart disease (CHD) in most industrialised countries during the latter part of the last century, CHD remains the leading cause of death among developed nations and is predicted to achieve that status worldwide over the coming decades (Tyroler, 2000). In addition, CHD is expected to become a major contributor to the global disease burden in adults, as measured in Disability Adjusted Life Years (DALYs) (Román, 2003).

Similarly, stroke constitutes a leading cause of death in adults worldwide and is currently the most frequent cause of disability in the elderly population (Di Carlo et al., 2000; Román, 2003). Although mortality from stroke may have declined following improved control of risk factors and therapeutic interventions, stroke-related morbidity has either remained constant or even increased (Di Carlo et al., 2000).

For symptomatic atherosclerotic disease in other arterial beds, including the lower extremities, lack of data on time trends in disease prevalence make it difficult to predict the morbidity distribution of these conditions. However, it has been pointed out that the increased survival of persons who otherwise would not have survived acute CHD or stroke will also lead to an increase in the prevalence of PAD, thus further contributing to the morbidity burden of older age groups (Fowkes, 2001).

This first chapter of the thesis presents a general background on atherosclerosis, its major clinical manifestations and risk factors. Following this is an introduction to the human brain, cognitive function, and the biological and pathological changes in cognitive function commonly observed in later life. Chapter two presents a critical review of published studies investigating the relationships between vascular diseases, CVD risk factors, and cognitive function in older people. Chapter three follows with the background and objectives of the present thesis. The methodology of the current study is described in chapter four. In chapter five the study results are presented while chapter six is a discussion of the main findings and methodological issues of the study. In chapter seven, the implications and recommendations for future research are detailed, followed by the study's conclusions.

1.2. ATHEROSCLEROSIS

1.2.1. Definition

Atherosclerosis is a progressive inflammatory disease of large and medium-sized arteries (Ross, 1999). Atherosclerosis is systemic in nature and broadly similar pathological features of the disease are commonly found in many major arteries, including the aorta, carotid, iliofemoral, and coronary arteries (Rauch et al., 2001). As a pathological entity, atherosclerosis has been recognized for more than a century. With rapid advances in both basic and clinical research over the past decades, important insights into its biological basis, risk factors, and clinical consequences, have been gained (Faxon et al., 2004).

Whereas the exact aetiology of atherosclerotic disease has yet to be revealed, various causal explanations have been formulated. For example, the response-to-injury hypothesis states that atherosclerosis constitutes a chronic inflammatory response of the arterial vessel wall to the injurious effects of atherogenic stimuli, such as elevated blood lipids, smoking, high blood pressure, diabetes, genetic factors, infectious agents, and/or other influences (Ross, 1999; Willeit and Kiechl, 2000). In particular, disruption of normal arterial endothelial function, rather than endothelial denudation as previously proposed, is now thought to be the pathophysiological hallmark of such an injury, and the first step of the atherosclerotic process (Ross, 1999).

1.2.2. Pathophysiology

Endothelial dysfunction induces a cascade of structural and functional alterations within the vessel wall of affected arteries. Characteristic of an inflammatory response, the adhesiveness of the endothelium to circulating leukocytes and platelets as well as its cell permeability to lipoproteins and other plasma proteins increases (Ross, 1999). Specific adhesion molecules displayed on the surface of endothelial cells have been found to be responsible for the adherence and migration of leukocytes (mainly monocytes and T lymphocytes) from the blood stream into the intima, the innermost layer of the arterial wall. Once in the vessel wall, the blood-derived monocytes (now called macrophages) express scavenger receptors for lipoproteins, enabling them to ingest lipids (Viles-Gonzalez et al., 2004). The presence of lipid-laden macrophages (now called foam cells) in the intima layer of the arterial wall forms the earliest lesion of atherosclerotic disease.

Further progression of early atherosclerotic lesions to so-called fatty streaks is dependent on the continuing accumulation of lipid-absorbing macrophages and smooth muscle cells which also contain lipids (Drouet, 2002). In most people, characteristic aortic fatty streaks may already be manifest by the time of adolescence (Velican and Velican, 1983). Programmed cell death (apoptosis) may be the eventual fate of many lipid-laden cells, leading to extra-cellular accumulation of lipids. Coupled with an increased synthesis, and reduced absorption, of collagen fibers by smooth muscle cells, the atherosclerotic lesion progresses from a fatty streak to an advanced atherosclerotic plaque which is characterized by a lipid core covered by a fibrous cap that walls off the lesion from the vessel lumen. This form of the lesion is thought to represent a type of healing or fibrous response to the initial endothelial injury (Ross, 1999).

The additional development of the advanced atheromatous plaque may depend on several factors, most notably its composition (Willeit and Kiechl, 2000). Continuous plaque growth occurs when atherosclerosis progresses slowly and equally across diffuse lesions, with the process relying on cumulative exposures to known atherogenic risk factors. In particular, high content of smooth muscle cells, a small lipid core, and a dense fibrous cap, are characteristic of stable atheromatous plaques. Importantly, in response to the gradual expansion of stable plaques, compensatory enlargement of the arterial lumen may occur through a process called 'vascular remodeling', whereby normal lumen is maintained during the disease course despite substantial plaque protrusion and stenosis. Although normal blood flow may continue uninterrupted, the stable plaque is of considerable clinical significance since most advanced lesions may undergo compositional changes, leading to greater lipid accumulation and thinning of the fibrous cap, making them become unstable and more susceptible to erosion, fissure, and even rupture (Newby et al., 1999).

Further to plaque compositional factors, inflammation (systemic and within the plaque core), cytotoxic substances released from inflammatory cells, blood cholesterol level, and mechanical and haemodynamic factors, have been implicated in increasing the vulnerability of the plaque to rupture (Willeit and Kiechl, 2000). When disruption occurs, resulting in a co-called complicated atherosclerotic lesion, the circulating blood is exposed to a variety of thrombogenic material, predisposing to atherothombosis. The extent of the resulting thrombotic response may vary greatly. For example, the thrombus formation may grow slowly and without clinical consequences in a circulation protected by extensive collateral circulation (Drouet, 2002). Alternatively, a major ischaemic event may occur. In addition to this classical form of thrombogenesis, microembolic particulate matter may spontaneously be released from within an active plaque over a period of hours, days, or weeks, which can lead to microvascular obstruction and clinically silent ischaemic infarcts (Drouet, 2002).

Despite some variation in lesion-structure by anatomical location, stemming from differences in local blood flow patterns, arterial wall structure, and the sensitivity and expression of ischaemia in distal tissues, the diffuse involvement of atherosclerosis has important clinical consequences (Drouet, 2002; Viles-Gonzalez et al., 2004). Specifically, an atherothrombotic event in one particular arterial site may imply that other territories in the body may already be affected by the same disease process (Dawson et al., 2002). This needs to be borne in mind throughout subsequent sections where the clinical manifestations of atherothrombotic disease in different arterial beds are reviewed.

1.2.3. Risk Factors

The main risk factors for atherosclerosis tend to be similar regardless of its anatomical location, even though some predilection of certain risk factors to the development and progression of atherosclerosis in different vascular sites is observed (Kannel, 1994). Extensive evidence shows that these factors are independent of the end organ supplied by a given arterial bed (Smith et al., 2004). In fact, much of the present knowledge of risk factors for non-coronary atherosclerosis in population samples is traditionally derived from studies of CHD.

Environmental as well as hereditary factors are important in the initiation and progression of atherosclerosis (von Eckardstein, 2005). These have often been divided according to their potential for modification and with respect to the strength of evidence in support of their role in the disease process (Goldstein et al., 2001). As a result, the major non-modifiable risk factors include age, sex, ethnicity, and family history. Further to this, several potentially modifiable atherosclerotic risk factors have been identified over decades of epidemiological study of atherosclerotic coronary disease. More recently, less well-established factors have been added to the list of potential risk candidates (Katzel and Waldstein, 2001). Associations between dyslipidaemia, hypertension, smoking, diabetes, obesity, physical inactivity, and certain psychosocial factors, and CHD have been well-documented. The above risk factors are presented in further detail below.

Non-Modifiable Risk Factors

The cumulative effects of ageing on the vascular system and the continuous influence of atherosclerotic risk factors over long periods of time are likely to contribute to the increased risk of CVDs with age. For instance, for each successive decade after age 55, the risk of acute cerebral infarction increases more than two-fold in both sexes. Disease incidence rates are generally higher in men relative to women even though comparatively more women die from CVDs each year because of their disproportionately longer survival into older age (Sacco et al., 1997).

Ethnic stratification of the incidence of cardiovascular disease and the risk of vascular-related mortality is well established. As an example, evidence has shown that within the US adult population, African and Hispanic Americans are at a greater risk of cerebrovascular disease than Whites (Goldstein et al., 2001). Chinese and Japanese populations are also found to have higher disease rates. A greater exposure to both genetic and/or environmental risk factors leading to obesity, hypertension, and diabetes, may in part account for such risk differentials. Inheritance of vascular risk factors, susceptibility to their effects, or shared cultural and environmental exposures, could also explain the role of family history in the increased risk of CVDs.

Major Modifiable Risk Factors

The role of abnormal blood lipid levels, including that of total cholesterol, low-density lipoprotein (LDL), and triglycerides, in coronary atherosclerosis is well recognized (von Eckardstein, 2005). However, the association of hyperlipidaemia with cerebrovascular disease remains unsupported even though a clear relation with carotid atherosclerosis, a major risk factor for cerebral ischaemia, has been found (Wilson et al., 1997). Similarly, the role of blood lipids in the development and progression of atherosclerosis in the periphery has not been confirmed (Vogt et al., 1992). Hypertension plays a major role in atherosclerotic disease, and has a positive, graded association with all main clinical manifestations. Thus, in addition to contributing to the progression of atherosclerosis, it can induce hypertrophy in the heart and may lead to cardiomyopathy and congestive cardiac failure (Messerli and Grodzicki, 1992). Hypertension is the single most important modifiable risk factor for cerebrovascular disease and the impact of antihypertensive treatment on the reduction in onset and mortality from cerebral ischaemia has been demonstrated in clinical trials (Dahlof, 2006). The role of hypertension in peripheral atherosclerotic disease may be substantial but remains somewhat undetermined.

The adverse effects of cigarette smoking on systemic vasculature and blood rheology make it an important risk factor for coronary heart disease. Most epidemiological evidence to date suggests smoking plays a major role in the development and progression of peripheral atherosclerosis, and in this respect, its influence in the periphery may be more important than in the coronary circulation (Vogt et al., 1992). Smoking has also been found to have a dose-response relationship with the risk of developing cerebrovascular disease (Munther and Rahman, 1998; Wolf et al., 1988). A clear reduction in the incidence of CVDs has been found following smoking cessation (Wannamethee et al., 1995).

Diabetes is associated with greater atherosclerotic risk and diabetic patients are found to have a higher prevalence of various atherogenic risk factors (Grundy et al., 1999). Diabetes is also related to a greater burden of CHD and may have independent influence on the incidence of cerebrovascular disease. Conflicting findings have been produced with respect to its role as a risk factor for PAD, but rather than increasing the risk of disease, it may contribute to occurrence of later-stage complications experienced by some patients (Fowkes, 2004).

The influence of body weight on CHD morbidity and mortality has been well documented (Alexander, 2001). Obesity is associated with greater prevalence of atherosclerotic risk factors, including hypertension and dyslipidaemia, and may increase the risk of cerebrovascular disease (Isozumi, 2004). In particular, abdominal obesity in men and weight gain in women may be associated with such elevated risk. Only weak data link obesity with PAD (Vogt et al., 1992). In a similar vein, the type and level of physical activity has been little studied in relation to peripheral atherosclerosis, but evidence points to beneficial effects of moderate, regular exercise on the development of cerebrovascular disease (Noda et al., 2005). Any protective effects of exercise may be mediated through its positive influence on the aforementioned atherogenic risk factors.

Other Modifiable Risk Factors

Both depressive symptoms and anxiety states have been found to be associated aetiologically and prognostically with increased CHD morbidity and mortality risk (Kubzansky et al., 1998; Rozanski et al., 2005). In contrast, their role in the development of other vascular diseases, including that of cerebrovascular disease, remains less certain. Possibly, an association of psychological states with atherosclerotic disease is mediated through negative health behaviours and accumulation of atherogenic risk factors (Kubzansky et al., 1998). Alternatively, the association may be explained by more direct influence of psychologically-induced biochemical and physiological changes affecting either the systemic vasculature or the blood (Stansfeld and Rasul, 2005).

Novel Risk Factors

More recently, there has been an increased interest in the potential role of several other risk factors for vascular disease, including serum and plasma levels of homocysteine, lipoprotein (a), and various inflammatory, rheological and coagulation factors. This has partly been because of recent developments in laboratory science contributing to the relative ease with which levels of these factors may be measured in large-scale population-based epidemiological studies (Whincup and Danesh, 2005). Moreover, the identification of new risk factors has provided opportunities for improving CVD risk predictions beyond that of conventional risk factors (Tsimikas et al., 2006).

Elevated serum levels of homocysteine, an amino acid formed during the metabolism of the essential amino acid methionine, have been found to be independently associated with an increased CHD risk in a dose-response fashion (Wald et al., 2005). Similarly, an association with the degree of atherosclerosis in the carotid arteries and the risk of overt cerebrovascular disease has been noted (Sacco et al., 1997). Levels of lipoprotein (a), an apolipoprotein homologous with plasminogen, correlate positively with the risk of developing CHD but studies are conflicting as to whether there may be a relationship with cerebrovascular disease (Goldstein et al., 2001).

Haemostatic and rheological factors, including plasma levels of fibrinogen and blood viscosity, have been found to be positively associated with an elevated risk of coronary and cerebrovascular events (Meade and MacCallum, 2005). Moreover, fibrinogen concentrations are related to the development and progression of PAD (Tzoulaki et al., 2006; Wildman et al., 2005). The contribution of fibrinogen to the risk of CVD may stem from its influence on blood viscosity, platelets, and its blood clotting potential (Sacco et al., 1997). In a similar vein, levels of circulating markers of systemic inflammation have been linked with an increased risk of atherosclerotic disease. In particular, C-reactive protein (CRP) and several pro-inflammatory molecules (e.g. various interleukins) may be related to acute coronary disease and possibly cerebrovascular disease as well. However, whether such inflammatory markers actually induce CVD or merely reflect vascular risk or subclinical atherosclerotic disease is still open to debate (Whincup and Danesh, 2005).

1.3. CEREBROVASCULAR DISEASE

1.3.1. Definition

The concept 'cerebrovascular disease' is used as a general term for describing abnormalities of brain structure and function of vascular causes. A major form of cerebrovascular disease is stroke, which has clinically been defined as rapidly developing signs of focal disturbance in cerebral function, with symptoms lasting 24 hours or longer with no apparent cause other than of vascular origin (Merino and Hachinski, 2001; WHO MONICA Project, Principal Investigators, 1988). With the increased sophistication and use of brain imaging techniques for early recognition and diagnosis of stroke, the presence of a defined lesion on imaging with corresponding symptoms was later been added as a criterion for diagnosing stroke (Boden-Albala and Sacco, 2004).

The clinical classification of stroke has been widely adopted in epidemiological research aiming at establishing the prevalence and incidence of stroke, but is limited with respect to two main aspects of the disease. First, it excludes a transient ischaemic attack (TIA) which can be regarded as a short-lived (most TIAs only last a few minutes) loss of function due to focal reduction in cerebral blood supply (Russell, 1983). Traditionally, it has been assumed that no structural brain damage has taken place after TIA, whereas in the case of a stroke, at least a minor ischaemic lesion remains. As indicated above, the distinction between TIA and stroke has been based on the duration of clinical signs. However, brain imaging has clearly demonstrated that it may be impossible to exclude cerebral ischaemia on symptoms alone. In fact, there seems to be no difference between a TIA and stroke with respect to aetiology, prognosis, and treatment (Russell, 1983). Second, from the sole use of the clinical definition, it may be difficult to establish the aetiology of stroke. For these two reasons, the term stroke has sometimes been used to denote any neurological dysfunction that is related to alterations of cerebral blood flow, irrespective of its duration or cause (Merino and Hachinski, 2001).

1.3.2. Stroke Subtypes

Three distinct aetiological categories of stroke are recognised (Boden-Albala and Sacco, 2004). The most frequent type is stroke caused by cerebral ischaemia which may account for as many as 70 to 80% of all strokes. To a lesser extent, intracerebral and subarachnoid haemorrhage make up approximately 15-20% and less than 10% of all strokes, respectively. Given the relative frequency and importance of cerebral ischaemia in the general population, the focus of the remaining text will be on stroke of ischaemic origin.

1.3.3. Pathophysiology

Several underlying pathophysiological mechanisms can lead to ischaemic stroke (Merino and Hachinski, 2001). In particular, large-vessel atherosclerosis commonly affects extra- and intracranial arteries. Advanced, vulnerable atherosclerotic lesions can be found in the carotid arteries in the neck and in the basilar artery, and sometimes in the middle and posterior cerebral arteries (see section 1.6.3. for a further discussion of the cerebral arterial vasculature). Where such lesions undergo plaque rupture and abrupt atherothrombosis, they may be manifested as large cerebral haemispheric or basilar artery infarcts. However, in the case of slowly growing stable plaques, leading to lumen stenosis, small reductions in systemic blood pressure levels can lead to cerebral hypoperfusion and ischaemia in vulnerable areas (so-called watershed areas). Atherosclerosis in large vessels may also lead to occlusion of the origin of smaller arterioles which penetrate the brain. Under these circumstances, small areas of infarction deep within the brain may occur, inducing symptoms characteristic of small-vessel disease (the occlusion of small arteries penetrating the brain may result in deep-lying infarcts, called lacunar infarcts. A wide range of clinical symptoms may be seen depending on the sub-cortical neural substrate affected, see Merino and Hachinski, 2001).

Further to atherothrombosis, artery-to-artery embolism also constitutes a major cause of acute ischaemic stroke. Despite the many potential origins of cerebral embolic material, the most common source in older people is an atherosclerotic lesion in one or more of the carotid arteries of the neck (Rook, 1999). In particular, the internal carotid artery leads directly to the middle cerebral artery which receives almost 80% of the blood traveling through the internal carotid. As a result, most emboli from the internal carotid artery have been found to have a predilection for lodging in the middle cerebral artery or one of its branches. Embolic material can also come from other extracranial sources, including a diseased heart. In particular, a frequent source of cardiogenic emboli is a thrombus lodged within the left auricle of dysrhythmic individuals, such as those suffering from atrial fibrillation (Bernhardt et al., 2006; Rook, 1999). A wall or mural thrombus formed on a hypokinetic endocardial segment following a myocardial infarction may also give rise to cerebral emboli. Other non-atheromatous embolic material, introduced through other means into the circulation, may also result in cerebral ischaemia.

1.3.4. Prevalence and Incidence

In most Western countries, stroke is a major cause of death and disability. Different sources of data may provide population estimates of the prevalence and incidence of stroke, including national statistics and population surveys. In the Health Survey for England in 2003, for example, 2.4% of men and 2.2% of women reported ever having had stroke diagnosed by a doctor with steeper rates observed at greater ages in both sexes (Joint Health Surveys Unit, 2003). In men, the prevalence rose from 1.2% in those aged 45-54 years to 7.5% men aged 65-74 years, and to 13.3% in those 75 years and older. For women, the proportions with stroke were 0.9%, 5.3%, and 8.8%, respectively. Overall, 0.4% of both men and women reported having had a stroke in the previous year. In the Scottish counterpart of the Health

Survey for England, very similar prevalence rates were reported (Scottish Executive Department of Health, 2005). In total, 2.4% of men and 2.1% of women noted ever having had a doctor-diagnosed stroke. Overall, 0.4% of men and 0.5% of women reported having had a stroke during the previous year. Age-specific prevalence rates for men were as follows: 0.9% in men aged 45-54, 5.9% in those aged between 65 and 74 years, and 11.3% in men 75 years and older. At every age, the prevalence rates for women were somewhat lower than for men or 0.5%, 5.0%, and 8.3%, respectively. More or less identical age and sex-specific prevalence rates have been reported in other Western populations (Thom et al., 2006).

A large body of evidence exists on the incidence of stroke and its relation with sociodemographic status, ethnicity, and geographical location, and more recently, stroke subtype (Boden-Albala and Sacco, 2004). Overall, the incidence of stroke is higher in men compared to women, and substantial geographical and racial differences are found both with respect to total stroke as well as specific subtypes. In the Rochester Epidemiology Project, a male/female ratio of 1.40 was noted for the four-year incidence of stroke when adjusted for differences in age structure (Petty et al., 1999). Similarly, in the Erlangen Stroke Project, a higher incidence rate was observed for men relative to women but this was only applicable to large-vessel stroke (22.6 versus 13.1 per 100.000 population) and small vessel occlusion (32.9 versus 27.1 per 100.000 population) (Kolominsky-Rabas et al., 2001). Greater cardioembolic stroke incidence was noted for women (44.5 versus 26.2 per 100.000 population in men). For all the stroke subgroups, however, the incidence rates increased steeply with age. Moreover, in the Northern Manhattan Study, Whites had lower incidence rates in all major stroke types relative to either Hispanics or African-Americans (White et al., 2005). Specifically, African-American subjects experienced the highest incidence rates irrespective of stroke type.

In a similar vein, vast differences in stroke incidence have been reported between countries and geographical regions (Thorvaldsen et al., 1995). Whereas some of the variation may be explained by heterogeneity in methodology, true differences in levels of exposure to risk factors are also likely to contribute to such patterns (Boden-Albala and Sacco, 2004).

1.4. CORONARY HEART DISEASE

1.4.1. Definition

The term 'coronary heart disease' covers a number of different clinical manifestations of ischaemia in the myocardium (Dawber, 1980). The main cause of CHD is atherosclerosis in the coronary arteries but the cardiac muscle is primarily dependent on the coronary circulation for its blood supply and normal functioning. In this respect, CHD is synonymous with the concept 'coronary artery disease'. It also embraces the term 'ischaemic heart disease', which is more specific than CHD since it highlights ischaemia as the underlying pathological mechanism (Tunstall-Pedoe, 1997). However, even though myocardial ischaemia most frequently is the result of atherosclerotic disease of the coronary arteries, it needs to be acknowledged that other pathomechanisms may also induce ischaemia in the heart (Tunstall-Pedoe, 1997; Stehbens, 1999).

1.4.2. Pathophysiology

As already discussed, the gradual build-up of atherosclerotic plaques in the coronary arteries may lead to narrowing of the vessel lumen. However, because of remodeling of the vessel wall, normal blood flow and perfusion of the cardiac muscle may be maintained despite a significant degree of arterial stenosis. More recent insights have moved beyond a notion of progressive occlusion due to lumen stenosis to one where it is recognised that coronary plaque vulnerability, predisposing to rupture and thrombosis, may be the lead cause of acute coronary syndromes (Viles-Gonzales et al., 2004). As a result, plaque composition, rather than degree of vessel narrowing, is likely to be a major determinant of CHD. Even though excessive propagation of atherothombosis may rarely take place, evidence shows that small, non-stenotic coronary plaques that have undergone rupture may be the cause of vessel occlusion in a significant number of acute myocardial infarction patients (Willeit and Kiechl, 2000). Indeed, a discrepancy between the amount of arterial wall affected by atherosclerosis and the clinical manifestations of CHD has been noted

(Dawber, 1980). Regardless of the process, however, ischaemia of the cardiac muscle is bound to occur when its demand for oxygen cannot be adequately met. If sufficient enough, the individual becomes aware of a definite feeling of discomfort in the chest, often radiating to the neck and down one or both arms.

1.4.3. Coronary Heart Disease Syndromes

Angina Pectoris

A transient shortage of blood supply to the myocardium may lead to the onset of angina pectoris, which is manifested as a dull or heavy discomfort in the epigastric area (Dawber, 1980). Typical of angina, symptoms appear with exertion, excitement, or emotional distress, accompanied by an increase in cardiac output. The discomfort characteristic of angina is non-specific to the disease and frequently experienced in other contexts. In clinical practice, a detailed medical history is commonly taken with respect to symptoms and precipitants of angina, and often the first step in the diagnosis is the exclusion of other differential causes of the symptoms. For epidemiological purposes, however, a clinical diagnosis of angina may not be reliable because of the subjectivity of symptom reporting. The application of electrocardiograph (ECG) at both rest and during exercise has been attempted in making the diagnosis of transient ischaemia more objective. Unfortunately, whereas a resting ECG may turn out to be normal, the use of exercise ECG is both risky and time-consuming and may not be suitable for population research. Moreover, ECG changes frequently observed in patients with angina have been found to be of limited diagnostic value (Chun and McGee, 2004). Other attempts to objectively diagnose the condition in population studies resulted in the development of a standardized, symptom-based angina questionnaire (Rose, 1962).

Myocardial Infarction

An MI occurs when prolonged ischaemia of a distinct segment of the cardiac muscle results in necrosis of that part of the myocardium (Dawber, 1980). Without exception, an MI is the consequence of atherothrombotic disease in the coronary circulation, and as already discussed, only a minimal arterial narrowing due to atherosclerosis may be present at autopsy (Dawber, 1980). Clinically, MI is characterized by the sudden onset of a severe substernal or epigastric pain which may radiate to the neck, jaws, and down the arms. In contrast to angina symptoms, the discomfort following an MI persists (or even becomes progressively more severe) and is neither relieved by rest nor administration of glyceryl trinitrate. In a small proportion of patients, no symptoms may have been experienced despite ECG evidence of a previous MI (Tunstall-Pedoe, 1997).

Alterations in ECG, including the presence of diagnostic Q waves and ST elevation, may be found during an MI, or alternatively, changes in ECG may evolve over hours and days following the event. As a result, recording of serial ECGs has proved to be valuable in the diagnosis of MI (Pope and Selker, 2005). The use of sensitive and specific biomarkers has also aided in the diagnosis of MI (Rajappa and Sharma, 2005). In particular, when necrosis of cardiac muscle cells occurs, several enzymes that are normally present in such cells are released into the blood. Tests have been developed to detect serum concentrations of different enzymes and an MI may be diagnosed when these are increased in the clinical context of acute ischaemia. While the enzyme concentrations are considered to reflect the extent of damage to the myocardium, they are unable to reveal the underlying cause (Alpert et al., 2000).

Chronic Heart Failure

Despite considerable aetiological heterogeneity, congestive cardiac failure is most commonly the result of CHD. The term refers to the inadequacy of the heart in maintaining the systemic blood circulation through its pump function (Crouch, 2005). Reduced cardiac output may lead to hypoperfusion of body tissues and organs. A number of different symptoms may be suggestive of congestive heart failure but most are non-specific to the disease (Khunti et al., 2000). In its most severe form, heart failure may lead to pulmonary edema which develops when inadequate cardiac pumping results in an increase in lung fluid secondary to leakage from capillaries in the lung into the pulmonary alveoli. An enlargement of the heart may also occur. In the Framingham Heart Study, the presence of pulmonary congestion and cardiomegaly by chest radiography, as well as ECG evidence of left ventricular hypertrophy, formed the basis for the diagnosis of congestive heart failure (Dawber, 1980).

Sudden Death

In Western countries, sudden death is most commonly a consequence of acute MI which may produce dangerous cardiac arrhythmia, such as ventricular fibrillation or asystole (Henkel et al., 2006). Although a majority of individuals who suddenly die have some evidence of CHD, such unexpected death frequently occurs in persons without previously-known coronary disease. Despite no standard definition of the term exists, the current practice of considering all such deaths as cardiovascular unless otherwise shown may be warranted (Dawber, 1980). On rare occasions, sudden death has seemingly occurred in the absence of CHD pathology. These are, however, found to be infrequent and unlikely to invalidate the classification of sudden death as a syndrome of atherosclerotic coronary disease.

1.4.4. Prevalence and Incidence

Population estimates of the prevalence of CHD have widely been collected. In data from the USA, age and sex-specific analyses showed significant differences in CHD prevalence rates between men and women and according to age (Thom et al., 2006). In both men and women, the prevalence rate rose steadily with every 10-year increase in age from the age of 35 years. However, at every age, the rates in men were up to three times as high as that for women. The highest rates for both sexes were seen among those aged 75 years and older, 16.8% for men and 10.3% for women, respectively. Substantially greater age-specific prevalence was noted in the annual Health Survey for England in 2003 (Joint Health Surveys Unit, 2003). In total, 6.4% of men and 4.1% of women reported having CHD (angina or MI). When broken down by age, those aged between 55 and 64 years of age (11.1% in men and

5.8% in women) had approximately three times higher prevalence of CHD than subjects aged 45-54 years (3.4% in men and 1.9% in women). In those aged 75 years and older, the prevalence increased to as much as 26.5% in men and 18.1% in women. Still higher rates of CHD were observed in the Scottish Health Survey, which found up to 31.7% of men and 22.9% of women aged 75 years or more to self-report either angina or MI (Scottish Executive Department of Health, 2005). Regarding specific CHD manifestations, 6.6% of men and 5.6% of women in total reported doctor-diagnosed angina whereas 4.2% of men and 2.4% of women had suffered an MI. Self-reported prevalence of both angina and MI increased steadily with age. Other manifestations of CHD, including congestive heart failure, have been found to follow a similar pattern as noted above with regard to age and sex despite evidence showing that elderly women may actually have higher prevalence of heart failure relative to men (Thom et al., 2006).

Incidence data of CHD tends to be based predominantly on the ascertainment of new cases of MI. Population estimates of event rates in different countries and regions have revealed vast geographical differences in the incidence of MI (Tunstall-Pedoe et al., 1999). In all countries, however, men are relatively more affected than women. Within the UK, large differences have been observed in incidence rates. Among the highest are those that have been observed in the Glasgow area, whereby an incidence of 777 per 100.000 population in men and 265 per 100.000 population in women, aged 35 to 64 years, was observed. In comparison, the rates in men and women of the same age in Oxfordshire were 273 and 66 per 100.000 population (Volmink et al., 1998).

Relative to MI, limited incidence data exists for other CHD syndromes. As expected, however, based on the few available studies in the UK, the incidence of angina has been found to increase with age and be higher in men compared to women (Petersen et al., 2004; Ghandi et al., 1995). Moreover, vast differences in incidence estimates exist across studies, possibly because of differences in populations or in methods for diagnosing angina. Similarly, few studies have investigated the incidence of cardiac failure, but in one UK-based study, the rate per 100.000 population was found to be approximately 50% greater in men compared to women at every age level over age 45 to 55 years (Cowie et al., 1999).

1.5. PERIPHERAL ARTERIAL DISEASE

1.5.1. Definition

The concept 'peripheral arterial disease', which is synonymous with that of 'peripheral vascular disease', mainly refers to atherosclerotic disease in the arteries supplying the upper and the lower extremities, and is much more rarely used to denote atherosclerotic disease in the carotid arteries of the neck. However, since disease in the upper extremities is proportionately rare, PAD is generally used to indicate atherosclerosis of the arteries supplying the lower limbs. In more precise terms, PAD refers to atherosclerotic disease of the distal aorta and the lower extremity arteries that induces lumen narrowing and disruption of blood flow in the legs (Fowkes, 2004).

Only when the atherosclerotic disease is relatively advanced, symptoms of ischaemia may appear. The most common clinical presentation of transient ischaemia in the lower limbs is intermittent claudication (sometimes referred to as angina of the legs), which is manifested as pain or tightness in the calf, or the thigh, on physical exertion and is relieved by rest (Dawber, 1980; Fowkes, 2004). Whereas most patients either improve with the disappearance of symptoms or stay about the same, comparatively few progress to more severe forms of the disease.

The clinical diagnosis of PAD is usually made on the basis of presenting symptoms (Fowkes, 2004). Similarly, self-reporting of symptoms has been used for epidemiological purposes in detecting atherosclerotic disease in the lower extremities (Dawber, 1980). For example, the WHO Intermittent Claudication Questionnaire has been widely used for the identification of symptomatic PAD in the general population (Rose, 1962). More recently, the Edinburgh Claudication Questionnaire was constructed with the aim of improving the validity of the WHO questionnaire (Leng and Fowkes, 1992). Further attempts have been made to provide more objective methods of diagnosing lower-limb atherosclerotic disease and several non-invasive tests may be used for confirming the clinical history. In this respect, measurement of the ratio of systolic blood pressure in the ankle to the upper arm (termed the ankle-brachial pressure index or ABPI), has commonly been used for the non-invasive assessment of PAD (Fowkes, 1991). Whereas an ABPI of less than 0.9 has been shown to be 95% sensitive and 100% specific in identifying angiogram positive disease in selective clinic samples, it may be less valid in establishing the presence of asymptomatic PAD in community-based studies. Other techniques have included palpitation of peripheral pulses, the use of stress tests, and Doppler ultrasonography (Fowkes, 1991). Moreover, arteriography, in which specific arterial segments can be directly visualized in living subjects, is currently the best objective method of quantifying atherosclerotic disease and is used as reference against which non-invasive techniques of existing disease are validated. However, apart from the ABPI, important limitations regarding validity, costs, and patient tolerance, have precluded most of these other methods from being widely used in population research.

1.5.2. Pathophysiology

The gradual progression of atherosclerotic disease from an early age in the distal aorta, the iliac, femoral, and popliteal arteries, may eventually lead to stenosis and ischaemia of the lower extremities (Dawber, 1980). As discussed earlier, at an advanced stage of atherosclerosis, ischaemic infarction may occur as a result of vessel occlusion, leading to tissue gangrene and necessitating amputation. There is evidence that atherosclerotic lesions at high risk of producing such acute ischaemic syndromes in the lower extremities may both be greatly stenotic and fibrotic (Viles-Gonzales et al., 2004). Further insights suggest that plaque stenosis, associated with a hyperthrombotic state of the systemic blood, plays a key role in inducing acute ischaemia of the lower limbs. Indeed, patients with advanced PAD have been found to have a high prevalence of vascular risk factors, such as smoking, dyslipidaemia, and diabetes, which increase the thrombotic potential of the blood (Willeit and Kiechl, 2000).

1.5.3. Prevalence and Incidence

A number of large-scale epidemiological studies have collected data on the prevalence of symptomatic PAD in different populations (Diehm et al., 2004). On many occasions, the WHO questionnaire has been administered for the purpose of determining prevalence rates of intermittent claudication. Prevalence estimates have been found to differ widely across studies, which in addition to true differences in levels of disease, might be explained by varying age distributions and other population characteristics (Vogt et al., 1992). Prevalence of intermittent claudication has been noted to increase with age in both sexes, and even though not always found, more men seem to be affected by the disease. In UK-based population studies, intermittent claudication was relatively rare among both sexes under the age of 55 but increased steadily thereafter (Bainton et al., 1994; Fowkes et al., 1991; Smith et al., 1991). Moreover, any male predominance observed in prevalence was found to decrease with increasing age. Whereas the WHO questionnaire has been found to underestimate the prevalence of PAD in the population, the Scottish Health Survey administered the Edinburgh Claudication Questionnaire which may be of better validity (Fowkes, 2004; Scottish Executive Department of Health, 2005). Overall, 2.8% of men and 3.5% of women were found to have PAD. In the oldest age category, among those aged 75 years and older, the prevalence was 8.9% in men and 6.9% in women.

The use of non-invasive measures has resulted in prevalence rates approximately 2-5 times higher than that observed using a symptom-based questionnaire (Vogt et al., 1992). Despite differences in absolute levels across studies, similar trends with respect to age and sex tend to be seen. In the Edinburgh Artery Study (EAS), for example, 17.0% of men and women had an ABPI of less than 0.9 (Fowkes et al., 1991). When a stress test was added, the prevalence rate of PAD rose to 24.6% for both sexes.

Data on the incidence of PAD has been collected less frequently than information on prevalence. Based on the available evidence, however, the incidence of intermittent claudication seems to increase with age in both sexes, and may be higher in men compared to women, although the gap narrows with greater age. For example, in the Speedwell Study in the UK, which only included men, 4.0% of subjects aged between 45 and 63 years developed claudication over 10 years of follow-up (Bainton et al., 1994). Moreover, in the EAS, substantially higher incidence rates were reported but approximately 9.0% developed incident intermittent claudication over five years of follow-up (Leng et al., 1996). The higher incidence rate in the latter study may be explained by the older study subjects as well as the inclusion of subjects having 'probable' intermittent claudication.

1.6. THE HUMAN BRAIN AND BEHAVIOUR

1.6.1. The Neuronal Basis of Brain Structure and Function

The central nervous system's (CNS) fundamental role is to receive, process, store, and communicate information (Lezak, 1983; Afifi and Bergman, 1998). Adequate exchange of information with the external environment is vital for normal functioning and survival. At the most basic level, the CNS comprises two distinct classes of cells: neurons and glial cells (Mitchell and Mayor, 1983). Whereas the role of glial cells is to provide support to neurons, the neurons themselves are responsible for information processing and communication. Despite many different types of neurons, all share common morphological features such as a cell body, single or multiple dendrites, and an axon (Kolb and Whishaw, 1996). The cell body, which contains the cell's nucleus and a number of intracellular organelles, is the centre of synthesis and transportation of proteins (called neurotransmitters) necessary for intercellular communication. The dendrites constitute extensions of the cell body, specialized in receiving information from other neurons in the form of electrochemical signals. The axon on the other hand, which frequently is wrapped in an insulating layer termed myelin sheath, represents the conduction component of the cell.

A small space or cleft, called a synapse, physically separates one neuron from another. When sufficiently stimulated, resulting in change in voltage charge across the neural membrane, a nerve impulse rapidly travels from the receiving sites of the neuron (mainly the dendrites but also the cell body) down along the axon. The propagation of the signal to other neurons is based on the release of neurotransmitters from the axonal terminal into the synaptic cleft. Consequently, these bind to specific receptors on the receiving neuron, and depending on the type of neurotransmitter, alter the post-synaptic neuron's behaviour in various ways. In addition to the unidirectional signal transmission across the synaptic cleft, other modes of information transfer exist, whereby neurotransmitters freely diffuse through the extracellular fluid from points that may be remote from the target cells (Coggan et al, 2005). It is thought that most cerebral functions use combinations of synaptic and 'extra-synaptic' transmission; whereas the former is fundamental to processes relying on great selectivity, rapid initiation, and quick termination (e.g. selective movements of the organism), the latter is likely to mediate general states of the organism such as sleep, arousal, and mood, that require both widespread and sustained neural activity (Kopanitsa, 1997).

The interaction of a single neural cell with other neurons (either across the synapse or through extra-synaptic transmission) forms the basis of all communication between neurons throughout the nervous system (Kolb and Whishaw, 1996; Afifi and Bergman, 1998). Despite their autonomy, however, neurons tend to operate collectively as assemblies or networks within the CNS, each of which makes a special contribution to brain functioning. Indeed, the vast number and heterogeneity of neuronal interactions is sufficient to provide the structural potential underlying the most complex and versatile aspects of human behaviour (Lezak, 1983).

1.6.2. Macroanatomical Features of the Brain

At the earliest stage in its development, the human brain may be divided into three anatomical structures: the hindbrain, the midbrain, and the forebrain (Gilman and Newman, 1992). In structural terms, the brain areas farthest back on the developing nervous system (the embryonic neural tube) are the most simply organized (Lezak, 1983). Moreover, with regard to their functional role in the nervous system, these are associated with the more primitive and often life-maintaining functions of the brain.

In the adult brain, the hindbrain represents the medulla oblongata (the centre responsible for the nervous control of respiration, blood pressure, and heart beat), the pons, and the cerebellum (together these other structures correlate information on physical posture and body movement). Located forward of the hindbrain, the midbrain contains further neural centres involved in the processing of sensory and motor (movement) information. Situated frontal to the midbrain, the forebrain presents a neural structure of vast anatomical complexity and versatility. The forebrain, which may be divided into two large cerebral hemispheres and other structures embedded deep within them (in particular, the thalamus and the hypothalamus), forms the functionally most advanced as well as the most recently developed part of the human brain (Gilman and Newman, 1992; Kolb and Whishaw, 1996). In contrast to the more primary functions mediated by the components of the hind –and midbrain, the forebrain is the centre of the highest functions underlying human behaviour (Lezak, 1983).

Collectively, the two cerebral hemispheres comprise by far the largest regions of the adult brain, amounting to approximately 80% of the total brain volume (Kolb and Whishaw, 1996). These are further made up of three principal features: the cortex, the white matter underlying the cortex, and several deeply-located neural centres called the basal ganglia, the hippocampus, and the amygdala (Mitchell and Mayor, 1983). The deep centres, or nuclei, as such collections of neuronal cell bodies deep within the brain are sometimes termed, serve important functions ranging from the regulation of movement (the basal ganglia) to memory processing (the hippocampus). The white matter under the cerebral cortex is made up of myelinated axons which look white or pale yellow on visual inspection and extensively traverse the brain. More specifically, these axonal projections (often in the form of bundles of many axons grouped together) are found to carry nerve impulses between neurons located in different cortical areas within the same hemisphere, between neurons in the cortex and the deep nuclei, or between the two hemispheres. As a result, the white matter may be seen as being responsible for the transmission of information between different areas of the brain.

In the cerebral hemispheres, the cortex represents the outermost layer of the brain. It is made up of four to six layers of neuronal cell bodies and their synaptic connections, and can be visually identified by its grey colour (often termed the grey matter) (Mitchell and Mayor, 1983). In humans, the external surface of the cortex is found to be highly convoluted, whereby grooves (sulci) separate the more elevated ridges (gyri). Even though the exact location of specific gyri and sulci may vary between the two hemispheres within the same individual, and between the brains of different individuals, consistently present sulci have been used in dividing the cortex into four areas or lobes that are named after the overlying cranial bones. Thus, the cortex is frequently subdivided into the frontal, temporal, parietal, and the occipital lobe (Kolb and Whishaw, 1996). The relationship of these regions with the functional output of the brain is discussed in detail in section 1.6.4.

1.6.3. The Arterial Vasculature of the Brain

Due to its vast metabolic demand, the brain depends on an uninterrupted blood supply which it receives from three major arterial systems: the right and left internal carotid arteries and the vertebrobasilar system (Waxman, 1996). More specifically, the vertebral arteries run upwards through the cervical vertebrae on each side of the neck and enter the skull through the skull-base opening where they eventually join to form the basilar artery which provides blood supply to the neural substrates of both the hindbrain (pons and cerebellum) and the midbrain. Further on, the basilar artery divides into two posterior cerebral arteries which irrigate the middle part of the temporal lobe, most of the occipital lobe, and deeper sub-cortical areas.

The two internal carotid arteries constitute major arteries of the neck and the head (Mitchell and Mayor, 1983). These arteries branch off the common carotid artery which, on each side of the body, directly leads off from the aortic arch. The internal carotids then ascend and enter the skull whereby they trifurcate into the anterior and middle cerebral, and posterior communicating arteries. While the anterior cerebral artery supplies blood to the middle portions of the cerebral cortex as well as to the anterior part of frontal lobe, the middle cerebral artery, found to be the largest of the three cerebral arteries, irrigates most of the frontal, parietal, and temporal lobes. Smaller arteries also branch off the middle cerebral artery to perforate the subcortical areas of the brain. The role of the posterior communicating artery is to connect the internal carotid and the middle cerebral arteries with the posterior cerebral artery.

1.6.4. The Brain and Cognitive Function

As suggested earlier, the division of the cerebral cortex into lobes is based on the visual presence of certain anatomical landmarks rather than specific structural or functional characteristics. At least in broad terms, however, this distinction has been found to provide a useful frame of reference for the localization of specific functions in the brain (Lezak, 1983). This is possible because in the cerebral cortex, certain functions have a primary or significant representation with enough regularity to be of value in clinical practice and research. For example, the frontal lobe is found to be involved in regulating and controlling intentions, and in programming and monitoring complex behaviour (Lezak, 1983). It can be further divided into three major functional zones, the motor cortex, the pre-motor cortex, and pre-frontal cortex. Each of these provides a neural substrate for distinct functions (Kolb and Whishaw, 1996). Much of the temporal lobe is involved in the processing of auditory and visual information, such as auditory memory storage and the organization of complex visuoperceptual information (Lezak, 1983). Within the temporal lobes, deeply-placed structures such as the hippocampus play a major role in specific types of memory functioning. Similarly, the parietal lobe may be divided into two functionally distinct areas, the anterior and the posterior parietal cortex (Kolb and Whishaw, 1996). Whereas the anterior part comprises the somatosensory cortex, which is responsible for sensations such as touch and pressure, the posterior part is concerned with processes related to spatial recognition, arithmetic, and reading. Finally, the most posterior part of the cerebral hemisphere is the occipital lobe, which is the site of the primary visual cortex (Lezak, 1983). As the name implies, the main function of the occipital lobe is vision, and within this region, specialised anatomical areas exist that are involved in the perception of form, movement, and colour (Kolb and Whishaw, 1996).

To reiterate, some cerebral lobes are mostly or entirely concerned with specific types of activity within the brain. In addition, most may also be further subdivided into smaller units or areas which may sub-serve different kinds of functions, and yet, the same lobal area may be involved in the processing of different information depending on whether it is on the right or the left side of the brain (Waxman, 1996). On the other hand, many aspects of brain functioning do not lend themselves to be identified within clearly demarcated neuroanatomical boundaries (Lezak, 1983). This applies especially to a wide range of complex or 'higher' cortical processes (cognitive functions), such as reasoning and judgment, abstracting, organizing, and planning, as well as specific aspects of these functions, all of which are likely to depend on the functional integrity of the entire neural substrate rather than on the intactness of discrete anatomical areas. In contrast, so-called 'lower' cognitive activities, an example being processes involved in the storage and recollection of information may be more easily correlated with underlying neuroanatomical structures.

1.6.5. Structural and Behavioural Consequences of Brain Damage

Injury to the brain may result from a number of different causes which may lead to short-term, intermediate, and long-term alterations in both brain structure and neurocognitive function (Kolb and Whishaw, 1996). Precisely what changes take place is likely to depend on many different factors. At the most fundamental level, however, there is likely to be immediate death of individual neurons which eventually may be replaced by a glial/connective tissue scar. Delayed neuronal death also occurs and is thought to involve different or additional pathophysiological mechanisms, including programmed cell death or apoptosis, which may continue for up to weeks following the initial insult (Mazarakis et al, 1997). Brain injury can also produce widespread physiological responses, which depending on the type of injury, may lead to brain swelling, changes in tissue metabolism and blood flow, and alterations in neurotransmitter release (Hacke et al., 1991). As a result, damage in one cortical area may not only lead to death of neurons locally but can result in temporary functional depression of other related areas in the brain; indeed, apoptosis has been described in sites distant from the initial focal damage (Mazarakis et al, 1997). As a consequence of neuronal death and axonal wasting, even very distal areas can undergo degeneration if they no longer remain connected and properly stimulated by the damaged area. Degenerative changes of distal areas may continue for months or years following the original insult.

The behavioural repercussions of damage to the brain will depend on a number of factors, including the nature, extent, and duration of the insult (Lezak, 1983). In addition, the individual's personal (e.g. age and educational level) and physical characteristics may further influence the observed pattern of cognitive impairment. As reviewed in later sections, the pattern of ischaemic structural damage and functional deficits is also likely to depend on which arteries are critically affected with atherothrombotic disease, or the final lodging site of embolic material.

1.6.6. Assessment of Brain Structure and Function

A number of methods are available for assessing brain structure and function. Largely for ethical and practical purposes, indirect methods of investigation tend to be used in studying the living human brain (Lezak, 1983). On occasions, direct brain examinations have been performed, either with surgery of neurological patients, or more commonly, by using animal models. However, given the limitations of such methods in generating comprehensive knowledge relevant to the normal human brain, this text emphasizes the more frequently used indirect methods.

Of the various techniques used in examining the structure of the brain, traditional radiography of the skull has been widely applied in clinical practice but less in the research setting. Employed in visualizing the structure and intactness of the cranial bones, some information about the intracranial anatomy can also be obtained (Bradshaw, 1989). Other useful neuroradiographic methods include pneumoencephalography (visualization of the spaces around and within the brain) and angiography (visualization of the blood vessels in the brain). However, given the invasive nature of these techniques, and the potential risks or complications associated with their use, their application in research has been limited.

As modern neuroimaging began to develop in the early 1970s, a whole new era in the investigation of the human nervous system began (Kolb and Whishaw, 1996). With the wide and rapid adoption of neuroimaging methods in both clinical and research settings, some of the older radiographic techniques were quickly replaced by these newer inventions. In particular, the computerised tomography (CT) allowed for the first time the creation of a visual representation of the brain (Hounsfield, 1973). The method involves a rotating x-ray source that takes multiple readings in a short period of time which are then translated by a computer into a transaxial photographic slice of the brain. The CT technique has a variety of applications, including the diagnosis of stroke, and in research of brain-behaviour relationships.

Despite being based on an entirely different principle, the invention of the CT contributed to the development of magnetic resonance imaging (MRI) during the 1980s (Bradshaw, 1989). As the name implies, MRI is based on measured changes in the resonance of hydrogen atoms in the brain under a magnetic field. The detection of radio waves emitted from these atoms allows the computation of images (even three-dimensional) of considerably better quality and detail than that produced by a normal CT scan. For example, MRI can provide information on specific neuroanatomical structures, including cerebral vasculature, far beyond what CT is capable of generating (Bradshaw, 1989). Unfortunately, the prohibitive cost of MRI has limited the number of population studies using this technique (Bradshaw, 1989).

Early methods for examining brain functioning include those that build on the brain's electrochemical activity (Kolb and Whishaw, 1996). As already mentioned, the activity of neurons has an electrochemical basis which may be recorded using specialised equipment. For example, by placing a number of electrodes across the scalp, small electrical changes in the underlying brain can be recorded and amplified to produce an electroencephalogram (EEG) (Afifi and Bergman, 1998). Clinically, EEG may be used to identify areas of brain pathology which are manifested as areas of localized slowing of EEG activity (Woodruff-Pak, 1997). Similarly, so-called event-related potentials (ERPs) represent short-lived changes in EEG signals in response to a specific sensory task or stimulus, such as a brief noise. Prolonged decision or processing time of any given task manifests itself as longer latencies of certain ERP waves (notably the so-called P300 wave) (Woodruff-Pak, 1997).

For a number of decades, positron emission tomography, or PET, has been employed in assessing the physiological response of the brain as it engages in cognition (Ramsey, 1987). This method is based on the idea that brain areas that are active will become more radioactive than less active areas and thus emit more positrons from radioactive isotopes ingested by the subject under study. Despite important shortcomings, including its invasive nature, studies have successfully used PET in elucidating brain mechanisms involved in age differences in cognitive function (Woodruff-Pak, 1997). Another technique, the single-photon emission computerised tomography, or SPECT, is based on the use of radioactive tracers which emit photons for determining in vivo body tissue function (Rahmim, 2006). Advances in detector technology and computing power have resulted in improvements in the spatial resolution obtained in SPECT imaging of the brain. However, in comparison to PET, as a technique, the SPECT is both less sensitive and has a lower spatial resolution (Spencer et al, 1995). A further elaboration of the MRI technique mentioned above is functional MRI (fMRI), which now is favoured over PET because of its patient safety and high resolution images (Woodruff-Pak, 1997). By detecting functionally-induced changes in blood oxygenation in specific areas of the brain, the fMRI can provide unique insights into cerebral functioning.

Standardised tests and questionnaires have been widely developed and used throughout the 20th century for assessing dimensions of human behaviour, especially those involved in the acquisition, processing, storage, organization, and communication of information. The emphasis on human cognitive processes may be attributed to the relative ease with which different aspects of mental function can be conceptualized, measured, and sometimes correlated with underlying neuroanatomical systems (Lezak, 1983). Indeed, on several occasions, currently available tests and measures (commonly referred to as neuropsychological, cognitive, or mental tests) have been derived and validated using comparisons between patients with circumscribed brain lesions and normal controls (Woodruff-Pak, 1997).

Neuropsychological tests have been applied in diverse settings for assessing patterns of mental function. In a clinical context, cognitive testing may be carried out in order to identify areas of strengths and weaknesses in intellectual capacity, to aid the diagnosis of underlying neurological pathology, or to make recommendations for treatment and care (Woodruff-Pak, 1997). Similarly, the goal of research may be to determine aspects of cognition that are disproportionately affected either by normal ageing or some pathological process. However, whatever the purpose, a comprehensive cognitive examination is likely to require the administration of multiple neuropsychological measures since individual tests are normally designed to assess a single major aspect or 'domain' of intellectual function.

The near-universal empirical finding that most representative mental tests tend to show a positive covariation may be considered as putative evidence of a common factor in all of the measured cognitive abilities (Jensen, 1998). In the early 20^{th} century, Charles Spearman suggested the term g (short for general intelligence) for this common factor (Spearman, 1904). His invention of the factor analytic method allowed the determination of the degree to which each of the cognitive measures correlated with (or loaded on) the general cognitive factor. More specifically, the general intelligence factor may be defined as the first unrotated principal component (or factor) from a battery of cognitive tests given to a study sample (Deary and Batty, in press).

The subsequent accumulation of cognitive test data as well as further sophistication of analytical techniques have preserved the central role of the general intelligence factor but also resulted in its modern conception (Detterman, 2006). For example, a hierarchy with the general factor at its apex and group factors (different groups of mental tests, each with similar task demands, may have these in common) at successively lower levels is at present the most widely accepted model of human cognitive abilities (Carroll, 1993). Further elaboration of the theoretical notion of the hierarchical structure of cognitive abilities led to the proposal of two yet substantially correlated aspects of general intelligence: fluid and crystallised abilities (Horn, 1994).

1.6.6. Structural and Functional Changes in Normal Ageing

Diverse changes in brain structure and function are thought to accompany normal ageing. In older persons, these are reflected in a number of measurable alterations in cerebral anatomy, physiology, and cognition (Raz, 2000). Although not firmly established, influences of both hereditary and environmental factors are likely to contribute to such observations. In particular, two major trends of structural and functional changes are commonly seen in the ageing brain: a selective preservation and decline against a background of global changes (Raz, 2000).

Generalised alterations in brain structure are found at both the macro –and microanatomical level (Duckett, 1991). For example, as people get older, the brain decreases in both weight and volume. The latter is demonstrated by an expansion of the spaces within the brain (ventricles) and an enlargement of cerebral sulci. The reasons for these structural alterations are not clear but may possibly reflect changes at the neuronal level, including reduction in the size and number of individual cells, and in the number of connections with other neurons (a process termed dendritic debranching) (Raz et al, 2005). Whereas it has been proposed that neuronal shrinkage may be a more decisive age-related change than actual cell loss, alterations in neuronal metabolism may also pose as a threat to the ageing brain (Stuart-Hamilton, 1991).

As mentioned above, some areas of the brain may be relatively more affected by the ageing process than others. For example, the cerebral cortex, and the prefrontal cortex in particular, may be especially vulnerable to the effects of biological ageing (Stuart-Hamilton, 1991; Raz, 2000). In comparison, age-related influence on other neural structures may only be mild (e.g. the hippocampus) or all together absent (i.e. parts of the hindbrain) (Raz, 2000). Further to changes in the brain's grey matter, the underlying white matter may also undergo both a decrease in total volume, which may be attributed to loss of neurons and demyelination. As with the grey matter, however, the white matter changes are unlikely to be equally distributed throughout the brain, and may in fact be restricted to certain cerebral circuits and axonal sizes.

Further to leading to macroanatomical alterations in the brain, the changes neurons go through as a part of biological ageing are also likely to be manifested in altered physiological functioning (Duckett, 1991). For example, a slowing of the dominant EEG wave rhythm with age is a well-documented finding even though it is not clear what it means in behavioural terms (Woodruff-Pak, 1997). Similarly, P300 latencies also tend to increase with age, suggesting information processing time may be slower in older persons (Stuart-Hamilton, 1991; Woodruff-Pak, 1997). More specifically, however, slowing in processing speed may be attributed to the time taken for the person to respond to a given stimulus (reaction time) rather than recognising it. This indicates that even within the domain of information processing speed, not all components may be affected equally or in a global fashion by the ageing process.

One fundamental reason for investigating age-related changes in brain structure and physiology is to shed further light on the similarly-occurring alterations in intellectual function (Raz, 2000). Thus, further to the relatively non-specific, age-related slowing of reaction times, three major patterns are found to characterise the process of cognitive ageing (see Salthouse, 1991 for review). First, supported by abundant empirical evidence, it has been pointed out that different types of mental functions may actually have different developmental trajectories which manifests as a pattern of differential decline on neuropsychological measures (Baltes, 1987). Indeed, specific cognitive processes, including reasoning, processing speed, working memory, and spatial ability, collectively referred to as 'fluid' abilities, may be particularly vulnerable to the effects of biological ageing but also neurological damage (Anstey and Christensen, 2000). However, findings from studies on the pattern of relations between age and cognitive measures representing distinct or separate 'fluid' mental functions suggest that most of the age effects may in fact be on the common factor or g and only a little on the factors specific to each of the 'fluid' cognitive tests (Salthouse, 2001). In other words, broad and relatively high-order influences appear to play a major role in the age-related effects on a wide variety of cognitive test variables. Although still open to debate, the commonality or generality of neuropsychological processing represented by the common cognitive factor may to a certain extent reflect the functional coordination and collaboration of multiple higher cortical networks that depend on the total integrity of white matter pathways linking diverse cortical and subcortical neuroanatomical regions (Newman and Just, 2005). In this regard, general cognitive function as captured by g is unlikely to be a single property of the underlying neural substratum (Detterman, 2006).

In contrast to the above, 'crystallised' functions, including general knowledge, vocabulary, and arithmetic, may remain stable, or even improve, through the influences of education and acculturation. Second, many of the intellectual abilities that decline with age seem to do so in a gradual, linear manner, and there is in fact little indication of abrupt transitions from stable to declining cognitive performance (Salthouse, 1991). Also, the process of cognitive ageing is marked by significant individual differences in both the level of cognitive ability and rate of decline. Indeed, depending on the cognitive outcome, chronological age has generally been found to explain less than one sixth of the total variance in cognitive test performance (which still may be substantial relative to the effects of many other factors) (Salthouse, 1991). Recent empirical data have further demonstrated a remarkable stability in individual differences in general intellectual ability over most of the lifespan (Deary et al., 2000).

1.6.7. Subclinical Cognitive Impairment

As discussed above, vast individual differences in levels of intellectual ability seem to accompany ageing. Characteristic of this spectrum of cognitive function in old age is that fact that, whereas some elderly experience no or only minimal change, others may deteriorate dramatically (Christensen, 2001). Moreover, in those who go on to develop dementia, there is likely to be a long pre-clinical or transitional phase of deterioration, which if amenable to intervention, may form a target for strategies aimed at either delaying or even preventing further decline and cognitive impairment (Bischkopf et al., 2002).

Over the past decades, several attempts have been made to describe the pre-clinical stage between normal cognitive ageing and dementia, which among other things, is reflected in the use of a somewhat confusing terminology. Thus, among the earliest descriptions of this intermediate period was 'Benign Senescent Forgetfulness' (BSF), which in fact was thought to be a variant of normal ageing rather than a distinct pathological entity (Petersen, 2004). This term was later followed by other but related concepts, including 'Age-Associated Memory Impairment' (AAMI), 'Age-Consistent Memory Impairment' (ACMI), and 'Ageing-Associated Cognitive Decline' (AACD), all of which tend to view cognitive impairment short of dementia to fall within the range of normal ageing (Bischkopf et al., 2002; Ritchie et al., 2001). Further conceptualizations of dementing disorders as disease processes, rather than the consequence of biological ageing, have stimulated the development of other categories, including 'Mild Cognitive Disorder' (MCD), 'Mild Neurocognitive Disorder' (MND), 'Cognitive Impairment, No Dementia' (CIND), and 'Mild Cognitive Impairment' (MCI) (Davis and Rockwood, 2004). In contrast to the previous concepts, these latter categories are assumed to be pathology-based and therefore amenable to treatment or prevention (Ritchie et al., 2001).

Relative to the other descriptions proposed above, MCI has widely been favoured as a diagnostic entity of subclinical cognitive impairment (Davis and Rockwood, 2004). Whereas the concept assumes a continuum between normal cognitive function and dementia of Alzheimer's type (AD) in particular, no single definition currently exists for MCI. In general, MCI is thought to refer to a group of individuals who have some cognitive impairment but of inadequate severity to meet diagnostic criteria for dementia (Petersen, 2004). Specifically, MCI was originally proposed if the following were present: 1) a memory complaint, preferably confirmed by an informant; 2) an objective memory impairment for age; 3) a relative preservation of other cognitive functions; 4) intact activities of daily living; and 5) no dementia (Petersen, 2004). Even though further expansions and refinements of the original diagnostic criteria have subsequently been undertaken (Portet et al., 2006), resulting in a shift from an emphasis on memory deficits to a focus on the general impact of mild dysfunction, the modified version continues to highlight the role of neuropsychological testing in the diagnosis of MCI.

As a part of the refinement of the original MCI concept, further sub-classification of the term has been carried out. The main reason for this breakdown in MCI is the fact that, whereas an increased progression to AD in MCI has been acknowledged, a substantial heterogeneity with respect to progression (not all MCI patients actually go on to develop AD) can be observed in many individuals with MCI (Davis and Rockwood, 2004). Thus, based on the type of neuropsychological profile, the following three clinical subsets of MCI, each of which may have different aetiological origins (and thus paths of progression), have subsequently been generated: 1) Amnestic MCI, which predominantly may lead to AD; 2) MCI with slight impairment in multiple domains, which may represent normal ageing, or progress to either AD or vascular dementia (VaD); and 3) MCI with impairment of a single cognitive domain other than memory, which may progress to various outcomes other than specifically AD (Petersen, 2004; Portet et al., 2006).

More recently, the term 'vascular cognitive impairment' was proposed to refer to all forms of mild to severe cognitive impairment associated with and presumed to be the result of cerebrovascular morbidity (O'Brien et al., 2003). The concept is, however, broad and there is much need for further refinement and identification of appropriate subtypes of vascular-based cognitive dysfunction.

Reviewers of studies of the prevalence and incidence of subclinical cognitive impairment have noted vast inconsistencies in findings across reports (Bischkopf et al., 2002). In particular, prevalence estimates differ greatly between studies due to different definitional criteria as well as different sampling and assessment procedures. As a result, findings are conflicting with respect to whether there is a continuous increase in the prevalence of cognitive impairment with age, and whether the estimates vary according to sex. Similarly, a comparison of incidence rates across studies is challenging due to an overall paucity of studies, differences in diagnostic criteria, sample structure, length of follow-up and cognitive measures. Thus, a steadily higher incidence of subclinical cognitive dysfunction with age, and among men, has been reported in some investigations (Bischkopf et al., 2002) but not others (Solfrizzi et al., 2004).

In an identical manner, data on the rate of conversion to dementia have been found to vary substantially between studies for similar reasons as above (Bischkopf et al., 2002). Of note is that the conversion rates to dementia seem to depend more on the diagnostic constructs used for subclinical cognitive impairment than any other factor, including the patient's age. For example, whereas studies using diagnostic criteria for BSF, AAMI, or MCD, have generally reported annual conversion rates to dementia or AD of less than 10%, somewhat higher rates have been observed in investigations where criteria for either AACD or MCI have been applied.

1.6.8. Dementia

Further deterioration in cognitive function may lead to dementia, which relative to normal levels of intellectual function, may be placed on the opposite end of the cognitive continuum. Dementia is not a single disease but refers to a syndrome that is characterized by a chronic or progressive deterioration in cortical and subcortical function that results in complex cognitive impairment (Ritchie and Lovestone, 2002; van der Flier and Scheltens, 2005). Moreover, diverse disturbances of mood, behaviour, and personality both frequently accompany as well as contribute to the dementia syndrome (Ritchie and Lovestone, 2002). Dementia is found to be of major public health importance as it is one of the most common diseases in the elderly and a major cause of disability, increased dependency, and death (Berr et al., 2005).

A wide variety of disease states may give rise to the clinical characteristics of dementia (Graves, 2004). Traditionally, the most common cause of dementia is AD, which typically begins with difficulty recalling recently learned material only to progress on to further loss of memory and decrements in various other cognitive and functional abilities. Although validated criteria have been developed for the clinical diagnosis of AD, the clinical evaluation is not definitive and needs to be supplemented with evidence of neuropathologic signs (the presence of neuritic plaques and neurofibrillary tangles in the brain is thought to be the hallmark of the AD pathology) at autopsy (Graves, 2004). In general, however, the accuracy (positive predictive value) of different clinical criteria for AD is found to be reasonably high (above 80%) when compared to a neuropathologic diagnosis (Graves, 2004).

A major form of non-AD type dementia is that of vascular origin. Possibly being an underestimation, the high prevalence of VaD in the older population is thought to be a reflection of the vast burden of cardiovascular disease in the elderly (Román, 2002). In particular, VaD was originally considered to arise from a series of discrete cerebral infarcts (the term multi-infarct dementia had been proposed), leading to a stepwise deterioration and deficits in frontal lobe executive function rather than predominantly in memory (Looi and Sachdev, 1999; Rockwood, 2002). However, it has become increasingly recognized that VaD may result from a wide variety of vascular lesions, including large -and small-vessel disease of extra –and intra-cranial arteries (van der Flier and Scheltens, 2005). Because of the heterogeneous nature of the vascular pathology underlying VaD, no single set of clinical criteria have become universally accepted for its diagnosis (Graves, 2004). Currently, the clinical diagnosis of VaD is based on patients having to fulfill criteria for 'dementia' and present evidence of cerebrovascular disease. Whilst this approach to the diagnosis of VaD is likely to be overly biased towards AD, emphasizing memory loss and progressive, irreversible decline as the primary symptoms (Rockwood, 2002), a clear separation between AD and VaD may not be possible in epidemiological investigations (van der Flier and Scheltens, 2005). A further complication to the study of specific dementia subtypes is the fact that different forms of the disease, such as AD and VaD, frequently co-exist in the same patient (referred to as mixed dementia) and possibly also sharing underlying risk factors and neuropathological features (Ritchie and Lovestone, 2002).

A number of studies have reported on the prevalence and incidence of AD and VaD according to clinical criteria alone and without neuropathologic confirmation. On other occasions, dementia as a whole has been the main focus of study. Based on such data, and despite the use of different methodologies for case identification and definition between studies, the prevalence and incidence of dementia has generally been found to increase steeply with age (Graves, 2004). For example, in an analysis of data from several European countries, the prevalence of dementia ranged from 1.2% to 4.7% among those 65-74 years of age, between 4.5% and 18.3% among those 75-84 years of age, and from 11.5% to 39.0% in those aged 85 years or above (Berr et al., 2005). An age-related trend in dementia prevalence was observed for both sexes. Similarly, among participants in the Cardiovascular Health Study, a steady increase in the incidence of dementia with age was noted in both men and women (Fitzpatrick et al., 2004). Whereas further analyses demonstrated a steep increase in the incidence of both AD and VaD with age, the incidence rates varied neither with sex or race. As discussed by Graves (2004), although several studies have similarly failed to find any gender differences in AD risk, there is evidence that women may be at an increased risk of AD. Even though the two genders may be at equal risk for developing AD pathology, generally lower education, social status, smaller head circumference and lower circulating levels of estrogens may place women at higher risk for showing clinical symptoms of AD and dementia (Graves, 2004).

CHAPTER TWO

Cardiovascular Diseases, Risk Factors and Cognitive Function

2.1. LITERATURE SEARCH STRATEGY

For the purpose of the present study the following bibliographic databases were comprehensively searched for relevant studies: *MEDLINE* (is the U.S. National Library of Medicine's premier bibliographic database that contains over 12 million references to journal articles in life sciences with a concentration on biomedicine dating back to 1966), *EMBASE* (a bibliographic database covering the worldwide literature on biomedical and pharmaceutical fields. It is published by Elsevier Science NY, the world's largest publisher of scientific information and its content covers information from 1974 to the present), and *psycINFO* (contains citations and summaries in the field of psychology and psychological aspects of medicine, psychiatry etc. Journal coverage, from 1887 to the present, includes international material selected from more than 1,300 journals written in over 25 languages. Over 55,000 references are added annually through regular updates). In addition, the following sources were used for identifying further research material: a) reference sections of studies identified through bibliographic search of the above databases, b) reference sections of relevant book chapters in *Neuropsychology of Cardiovascular Disease* (Waldstein SR and Elias MF (Eds). New Jersey: Lawrence Erlbaum Associates, Publishers, 2001), c) reference sections of relevant book chapters in *Medical Neuropsychology* (Tarter RE, Butters M and Beers SR (Eds). Luwer Academic/Plenum, Publishers, 2001), d) the reference section of *Neuropsychological Function in Patients with Peripheral Vascular Disease* (Unpublished doctoral dissertation, Dalhousie University, Halifax, Nova Scotia, Canada), and e) the reference section of *Risk Factors for Dementia and Cognitive Decline* (NHS Health of Scotland source document compiled by Gow J and Gilhooly M, October 2003).

In particular, *MEDLINE* was searched from 1966 to present (September 2005). Similarly, *EMBASE* was searched from 1980 to present. The *psycINFO* database was searched from 1990 to present. The literature search was limited to research material published in the English language. As an example of the search terms and combination of terms used, the following search string was generated for identifying published studies in *MEDLINE* on the association between CHD and cognitive function:

("coronary heart disease" OR "coronary artery disease" OR "heart disease" OR "angina pectoris" OR "myocardial infarction" OR "heart attack") AND ("neuropsycholog$" OR "cognitive function$" OR "cognitive performance" OR "cognitive decline" OR "cognitive change" OR "cognitive impairment").

All studies identified through the above methods were entered and stored using bibliographic computer software. Given the relative scarcity of studies in this field, criteria for the inclusion/exclusion of studies were kept necessarily broad. As a result, the following pre-determined criteria had to be met in order for the CVD and vascular risk factor-based studies to be included in the present review: a) observational epidemiological design (i.e. cross-sectional, case-control, cohort), b) structured neuropsychological test (rather than solely clinical evaluation of cognitive impairment/dementia), c) sample based on adult subjects (middle-aged or older) at the time of (follow-up) cognitive testing. The subsequent appraisal (particularly that focusing on the potential validity of the reported results and the role of chance, bias, and confounding as alternative explanations) of individual reports was in line with suggested criteria for the evaluation of published epidemiological studies (Fowkes and Fulton, 1991).

2.2. COGNITIVE FUNCTION AND STROKE

2.2.1. Introduction

Diverse neurological symptoms may occur following the cessation of blood flow to the brain. Specifically, both long-lasting sensorimotor and behavioural (e.g. language) disturbances are frequently observed in the aftermath of acute cerebral ischaemia. Moreover, it is well recognised that either a single major or repeated strokes may increase the risk of mild to severe cognitive impairment, hence the term multi-infarct or vascular dementia. In contrast, until recently, reviewers have noted a relative paucity of research into the frequency, severity, and patterns, of neuropsychological deficits in relation to stroke as a clinical entity.

The present chapter provides a review of studies investigating the relationship between stroke and cognitive function. In particular, an attempt is made to answer the following questions: is stroke negatively associated with performance on neuropsychological tests? If so, do stroke patients show a generalised pattern of cognitive impairment or are certain aspects of cognition more affected than others? Also, does stroke predict decline in cognitive test performance? In recognition of the pathological and clinical diversity of stroke, a further review is offered on findings from studies examining the influence of these and specific patient characteristics on post-stroke cognitive function. Lastly, a methodological discussion of current studies is provided. An overview of the reports reviewed in the text is provided in appendix A-1.

2.2.2. Mechanisms of Neurocognitive Dysfunction and Stroke

As already highlighted in the text, the behavioural sequelae of stroke are likely to be associated with many factors, not least its location within the nervous system. In the brain, ischaemic stroke may be confined to the cerebral cortex, the underlying white matter, or both (Merino and Hachinski, 2001). Large-vessel atherosclerosis of intra and extracranial arteries may lead to cerebral hypoperfusion and commonly results in artery-to-artery embolic stroke. Even though the differentiation between an embolic and non-embolic ischaemic stroke may be difficult, embolism may be inferred where, in the absence of an identifiable cardiogenic source and complete carotid occlusion, there is onset of non-progressive, rapid symptoms of cortical dysfunction that depend on the area affected (depressed consciousness may also occur). For instance, infarction of the area supplied by the anterior cerebral artery may result in defects in prefrontal lobe function, including perseveration and disturbed temporal memory (Kolb and Whishaw, 1996). Similarly, an ischaemic injury to the territory supplied by the middle cerebral artery, the largest of the three cerebral arteries, may present as deficits in frontal, temporal, or parietal lobe function. Thus, very heterogeneous behavioural effects may be seen, ranging from contralateral disturbances in sensorimotor functioning, impairment in language ability (left-sided lesions), to apraxia and impaired spatial ability. Finally, ischaemia in the area supplied by the posterior cerebral artery may manifest as inability in reading and in naming objects.

Ischaemic damage to the sub-cortical white matter may arise from atherosclerotic occlusion of the origin of small perforator vessels of the brain (Merino and Hachinski, 2001). Without intact white matter connections, cortical as well as deeply-located neural areas are unlikely to fulfil their functional role.

2.2.3. Frequency of Cognitive Impairment, Patterns of Cognitive Function, and Stroke

Evidence from clinic-based samples

To date, the majority of reports of the association of stroke with cognitive function in older adults have been based on samples of consecutively admitted hospital patients. In different studies, the cognitive assessment has been carried out at variable time-points following the event. On a number of occasions, performance on global cognitive tasks has been used in estimating the degree of generalised cognitive dysfunction in these patients. Alternatively, established diagnostic criteria or composite test scores have been employed, whereby performance below a certain cut-off level has been used to denote cognitive impairment. Based on such data, there is evidence to suggest that as much as over one third of patients may experience deficits in global cognitive function at various time points after stroke. For example, Ballard et al. (2002) found approximately 32% of 150 elderly stroke patients, aged 75 years and older, to meet diagnostic criteria for "Cognitive Impairment No Dementia (CIND) three months after stroke. All patients, who were recruited from a hospital-based stroke register, were considered free of dementia at the time of cognitive testing (according to DSM-IV criteria), as well as without disabilities such as aphasia and hemiparesis. In an early study by Tatemichi and colleagues (1994), over 35% of elderly patients were found cognitively impaired at three months, based on their performance below the fifth percentile of the residual scores of controls on four or more cognitive measures. In comparison, only 3.8% of controls were cognitively impaired when age, sex, race, and education, were statistically controlled for. Importantly, in the light of the fact that a number of abilities, including vigilance, language, attention, and sensory and motor skills, may be acutely depressed following stroke, and thus potentially affecting patients' early cognitive test performance, both studies used an interval of three months from the onset of stroke to the time of cognitive assessment.

The timing of cognitive assessment may have implications for the longitudinal study of cognitive function after stroke, since by testing patients early post-stroke, greater improvements in global function may be observed over time. In a report by Rasquin et al. (2004), 44.3% of 196 elderly patients (mean age of 68.5 years) were defined as cognitively impaired one month after a first-ever stroke. Cognitive impairment was defined as a baseline CAMCOG score below the 10th percentile of the performance of a population-derived control group, matched on age, sex, and level of education. At six months post-stroke, however, 33.5% of patients still had cognitive impairment. Still later, at 12-month follow-up, an almost identical proportion of patients (33.8%) were found to have global cognitive impairment. Whereas selective participation at follow-up cannot be excluded, no baseline differences in mean MMSE (Mini-Mental State Examination) scores were found between subjects who continued in the study and those who did not (about 20% of patients).

Further evidence was provided in a study by Ballard and colleagues (2003). In contrast to the previous one, which examined the proportion showing impairment at different time points, this study analysed the actual intra-individual change in test scores over the follow-up period. Based on a sample of 115 very old stroke patients, recruited from a hospital-based stroke register, the investigators showed that 31% of patients experienced a drop in mean MMSE scores, from 26.6 to 24.1. Conversely, 57% had an increase in MMSE scores (mean increase of 2.2 points, from 24.6 to 26.8). Moreover, of those who demonstrated an increase, 18 subjects actually had an increase of more than 2.2 points. However, the remaining 36 subjects had modest increases of 1 or 2 points. All in all, 76% of these very old stroke patients remained stable over the follow-up period, that is, neither improved nor declined.

The use of specific cognitive tests has provided data on the pattern of neuropsychology in stroke patients. Particularly in the early stages after acute stroke, very high rates of impairment have been observed across different cognitive domains. For example, in a study by Riepe et al. (2004), approximately 77% of 209 elderly ischaemic stroke patients, who were tested within 24 hours of admission, were found to be impaired in concentration and working memory, while 73% scored below the cut-off score for impairment in total memory (both free and cued recall of four items was assessed). Moreover, about 45% had impairment in the ability to name objects presented on pictures (11 of 12 items was defined as cut-off); 25% were impaired on the 'orientation subscale' (patients needed to answer at least 7 of 8 questions regarding person, time, and place) of the Alzheimer's Disease Assessment Scale (ADAScog). Thus, early in the aftermath of stroke, a high percentage of patients may fall below defined criteria for impairment on apparently simple cognitive tasks, taking only a few minutes to complete. However, since patients were assessed within hours of stroke onset, potential confounding by acute post-stroke confusional state or sensorimotor deficits cannot be ruled out. Even though a further three-month examination suggested the persistence of cognitive deficits across all domains apart from orientation, the validity of the data may be questioned since complete data were available for less than 25% of the baseline sample.

In another study, Hochstenbach et al. (1998) found up to 70% of 229 consecutively admitted elderly stroke patients to be impaired in attention and information processing ability when clinical criteria for impairment were used (defined as a score below the 15^{th} percentile of the performance score of a group of 33 healthy controls, comprising the patients' spouses and community recruits). With respect to attention, these are substantially higher rates than in the study reviewed previously, and may partly depend on the more sensitive instruments used in this analysis. In addition, when more rigorous statistical criteria were applied (defined as performance greater or less than 2 standard deviations of that of controls), almost 50% of patients still had impairment in these same functions. Similar rates of impairment were observed for visuospatial and constructive skills, but memory functions, and particularly those involving short-term recall of verbal material, seemed to be less affected.

Even though a majority of stroke patients may show impairment across cognitive domains, some functions may be relatively less affected than others. Moreover, this pattern may become more evident as the time interval between the onset of stroke and cognitive testing increases. In this respect, the two studies above were found to differ substantially. Whereas in the former study patients were cognitively tested within 24 hours of admission for acute stroke, in the latter, in which relatively few stroke patients had impaired memory, the average interval between stroke and cognitive testing was approximately two months. Further supporting evidence come from a recent analysis of the Göteborg 70+ Stroke Study in which 149 non-demented elderly participants were cognitively assessed 20 months after an index stroke (Lindén et al., 2004). In comparison to age-matched community controls, approximately 17% of patients were found to be impaired in non-verbal mental abilities as assessed by the ADAScog. In comparison, less than 9.0% of controls had deficits in these domains. However, whereas more stroke patients (5.6%) than controls (2.2%) had impaired memory (based on items assessing short, intermediate, and long-term memory), the proportion having impairment in memory function was substantially lower than that noted for the other cognitive domains.

The collection of longitudinal data on neuropsychological test performance has provided valuable insights into the long-term cognitive outcomes following stroke. However, so far, these have both been limited in number and resulted in mixed findings. For example, Rasquin et al. (2002) showed how 52.1% of 139 elderly first-ever stroke patients, cognitively assessed one and six months post-stroke, improved by more than 10 points in total verbal memory score over the five-month study period. In comparison, 37.6% remained stable and 10.3% declined by the same amount. Importantly, only 22.2% of the patients were considered impaired in memory at baseline, a substantially lower proportion than was found to be impaired in either information processing speed or cognitive flexibility (49.6% and 45.8%, respectively). Moreover, relative to those with memory deficits, fewer patients who were impaired in these functions improved (37.2% and 41.8%, respectively) and more declined (12.4% and 13.6%, respectively).

In a subsequent study by Rasquin et al. (2004), already described earlier in the text, similar patterns as above were observed. In this study, the proportion of patients showing impairment in verbal memory was reduced by 36.9% over the one-year study period. In comparison, the proportion of patients having deficits in executive functions, non-verbal ability, cognitive speed, and attention, decreased by 30.8%, 28.2%, 17.9%, and 4.4%, respectively. In stark contrast to these findings, Sachdev et al. (2004) failed to find any evidence in support of preservation of memory functions in a sample of 123 elderly stroke/TIA patients. In fact, by examining the one-year individual change in cognitive scores, stroke patients were found to have significantly steeper decline in both verbal memory and visuoconstructive ability scores relative to 78 community controls. Importantly, the analysis controlled for age, education, and MMSE score at baseline, and the size of effects was found to be equivalent to that of 14 and 21% of a standard deviation, respectively. However, perhaps somewhat surprisingly, and in further contrast to previous findings, stroke patients did not decline at a greater in information processing speed, attention, non-verbal reasoning, or executive control function, compared to healthy controls.

Evidence from population samples

Studies of the cognitive performance of community-recruited stroke survivors suggest impairment may be frequent in individuals who generally may be considered as having milder stroke pathology compared to hospitalised patients. Thus, Patel et al. (2002) found 38% of 248 elderly patients to score less than 24 on the MMSE three months after a first-ever stroke. Zhu and associates (1998) had shown earlier that the presence of stroke was associated with significantly increased odds of cognitive impairment, also defined as an MMSE score less than 24, in a study of 1810 community-based residents, aged 75 years and older. Specifically, when statistically controlling for potential confounding by age, sex, education, systolic blood pressure, antihypertensive use, and heart disease (ICD-8 codes 390-429), the association between stroke and global cognitive impairment persisted (OR=2.4). In approximately 58% of stroke patients, the index event had occurred more than three years prior to cognitive testing (in 37.9% and 14.4% of patients, the index stroke had taken place more than five and 10 years earlier, respectively).

In addition to reduced performance levels, stroke subjects may also be at an increased risk of decline in global cognitive function as demonstrated by Kalmijn et al. (1996), who found elderly male stroke subjects in the Zutphen Elderly Study at 4.3 times increased odds of having declined over three years (1990 to 1993). The effects were independent of age, education, and baseline MMSE test scores. These results are probably an underestimation of the true effect size because of the selective follow-up participation of subjects who both had higher MMSE scores and were less likely to report history of stroke at baseline. Further underestimation of the true effects is likely to stem from the fact that non-stroke TIA subjects, as opposed to stroke survivors only, were included in the study. In the Framingham Study (Kase et al., 1998), a group of 74 first-ever incident stroke patients was found to score slightly less on the MMSE at baseline relative to stroke-free controls (mean MMSE score of 27.3 versus 28.1). At six months post-stroke, the differences between patients and controls had become even more pronounced (those with stroke had a mean score of 23.6 compared to 28.3 of controls). Whereas the comparison was matched for age and education, the study did not control for either baseline differences in baseline MMSE performance or risk factors for stroke. This would, however, have been necessary in order to accurately assess differences in rates of decline, particularly given the fact that the patients' cognition levels were already compromised at baseline (pre-stroke). Moreover, by this time, the stroke subjects also possessed a significantly more unfavourable 'stroke risk profile', expressed as the 10-year probability of having stroke.

In most of the population-based stroke studies to date, there has been a trade-off between using a large sample size, and thus providing adequate statistical power, and the ability to gather comprehensive neuropsychological test data. Limited empirical information currently exists with respect to the extent and patterns of domain-specific cognitive impairment in survivors of stroke. Moreover, on several occasions, these have proved to be contradictory across studies. Specifically, whereas some studies have shown greater levels of deficits in specific cognitive domains in subjects with stroke, other investigations have failed to provide evidence in support of this. For example, a cross-sectional study by Srikanth and colleagues (2003) found no statistically significant differences in mean cognitive test scores at three months, when 99 non-aphasic, first-ever stroke survivors were compared to 99 age -and sex-matched community-derived stroke-free subjects. This was despite the inclusion of people with both definite ischaemic and haemorrhagic stroke (those with TIA/possible stroke were excluded). Relative to controls, however, the stroke patients had 50% increased odds of impairment in any cognitive domain (defined as a more than one domain-specific test score below one standard deviation of the performance of controls), which was primarily attributed to deficits in a single, rather than multiple, cognitive function.

Similar findings were reported for 1224 older adults in the Longitudinal Aging Study Amsterdam (LASA), who were cognitively tested on two separate occasions, at baseline and three years later (Dik et al., 2000). When compared to stroke-free subjects, and adjusting for age, sex, education, and baseline test performance, patients with stroke did not show on average a faster decline in either immediate or delayed verbal memory, or information processing speed. Identical results were observed when the odds of three-year decline in the above functions were compared in patients and controls.

Particularly with respect to cognitive speed, the above results contrast with that of an earlier report from the Cardiovascular Health Study (CHS) (Haan et al., 1999). In this investigation, elderly subjects with prevalent stroke declined faster over a period of seven years in mean Digit Symbol Test scores, relative to stroke-free participants (-1.96 points compared to -0.28). This analysis controlled for age, sex, race, education, and incident stroke, and similar effects of stroke were seen for the MMSE (-4.47 points versus -0.64). Whereas the sample size of 5888 subjects was considerably larger than that used in the studies described previously, the follow-up period was also substantially longer. However, tasks assessing other cognitive domains, including aspects of memory functions, were not administered in this study.

2.2.4. Stroke Characteristics and Cognitive Function

As reported in the previous section, impaired performance on both global and domain-specific cognitive tasks may frequently be observed in stroke patients. Both clinical and population-based investigations have, however, also demonstrated that not all patients are likely to show impairment in mental function. But even under such circumstances, a substantial proportion of stroke patients may still experience some recovery in neuropsychological function with time. In this respect, it is possible that the pathological heterogeneity of the event may have important prognostic implications regarding the level and progression of cognitive dysfunction following acute stroke.

On the whole, relatively few reports have examined the prognostic impact of different anatomical features of stroke on cognitive performance. Despite the challenges in accurately classifying stroke according to subtype and pathological characteristics, several studies have provided data on some aspects of the type of stroke, its laterality, location, and/or lesion size. The overall scarcity of reports has hindered the synthesis of findings from such studies, which in addition are frequently found to contradict each other. In particular, it is not clear whether stroke type is associated with greater or lesser degree of cognitive impairment following such an event. For example, Patel and colleagues (2003) found no effects of stroke type, based on the Oxfordshire Community Stroke Project (OCSP) Classification, on the proportion of patients showing recovery from MMSE-based cognitive impairment over a period from three months to one year post-stroke. Similarly, no differences with regard to stroke type were reported in a clinic-based study of 237 stroke patients (180 with ischaemic stroke and 57 with haemorrhagic stroke), in which those with memory deficits were compared to those without such impairment (Madureira et al., 2001). Moreover, when the analysis was extended to stroke patients with any cognitive dysfunction, relative to those without such deficits, no differences with regard to stroke type were noted. In contrast to these null findings, Zhou et al. (2005) demonstrated that, compared to elderly stroke subjects who were found cognitively intact at three-months post-stroke (based on MMSE performance), those with impairment were more likely to have had embolic cerebral infarction. Of the 70 ischaemic stroke patients in the Framingham Study (Kase et al., 1998), those with thrombotic non-lacunar or cardioembolic stroke were found to experience a faster decline in MMSE scores relative to lacunar stroke patients (4.0 and 4.4 versus 1.4 MMSE points, respectively). The differences failed, however, to reach statistical significance.

Further to the above, Hochstenbach et al. (1998) divided cognitive tests into two clusters according to whether a verbal or non-verbal response was needed in order to complete the tasks. The verbal cluster contained tests such as the AVLT, WAIS similarities, and a test of verbal fluency, while the non-verbal part included the WAIS Digit Symbol Test, Digit Span, Block Design, and clock drawing. Using a summary score for each data cluster, no multivariate effects of stroke type were found for the verbal scores, whereas cerebral infarction, rather than haemorrhagic stroke, was associated with a better non-verbal performance. However, since these effects were attributed to better performance on only three out of 17 tests, further research was suggested by the authors in order to clarify whether stroke type actually makes a difference for the prognosis of post-stroke cognitive impairment.

Similarly, stroke laterality has been studied in relation to post-stroke cognitive function in several investigations, and even though in a majority of investigations dominant hemispheric stroke has been found to be associated with poorer cognitive outcomes, not all studies have reached such a conclusion. Thus, in the aforementioned study by Patel et al. (2002), both bilateral and left hemispheric stroke was associated with greater prevalence of cognitive impairment three months post-stroke. This was also demonstrated by Zhou et al. (2005), and in an earlier study of 227 elderly stroke patients, left-sided stroke, relative to either non-dominant or vertebrobasilar stroke, was related to greater impairment in cognitive function (defined as a performance score on four or more cognitive tests below the fifth percentile of that of demographically-matched controls) (Tatemichi et al., 1994). Similarly, the Framingham study showed that patients with left-sided stroke declined at a greater rate in global cognitive scores in comparison to non-dominant stroke patients (4.38 versus 1.65 MMSE points), albeit the difference did not reach statistical significance. Hochstenbach et al. (1998) noted moreover that left-sided stroke was associated with worse performance in cognitive abilities requiring both verbal as well as non-verbal response. This finding suggests that even though the left hemisphere is considered dominant for language and intellectual functions, a wide range of non-verbal disturbances in mental function can also arise from damage to specific left-sided cerebral structures and associated neural connections.

In contrast to these results, Desmond et al. (1996) compared ischaemic stroke patients who had improved (defined as increase in composite cognitive score of more than two standard deviations above the mean first annual control group change) to those who had not shown improvement over a nine-month period following stroke. In this study, improvement was found to be significantly related to left hemispheric infarction relative to either right hemispheric or vertebrobasilar stroke. In a similar vein, Patel et al. (2003) observed less cognitive recovery in left-sided stroke patients, but a comparison with those with right hemispheric stroke turned out to be non-significant. In the study by Madureira and colleagues (2001), dominant hemispheric stroke was found to be more common in stroke patients with memory deficits, compared to those without, whereas any cognitive deficit was noted to be more frequent in right hemispheric stroke patients.

In comparison to the data available on both stroke type and laterality, substantially less information is available on other aspects of the event in studies of cognitive function post-stroke. However, based on findings from only a few studies, stroke severity seems to be associated with poorer cognitive outcomes. For example, Tatemichi et al. (1994) found that large lesions, independent of laterality, were associated with greater frequency of cognitive impairment three months post-stroke. Also, anterior (frontal/medial lobes) and posterior (parietal/occipital/temporal lobes) arterial infarcts were related to more global cognitive impairment than vertebrobasilar (brain stem/cerebellum) arterial strokes. In the Framingham study, Kase et al. (1998) observed steeper decline in global function in patients presenting with large infarcts, involving more than one half of a cerebral lobe. In contrast, neither the location nor severity, or the number of infarcts and the interval from stroke to cognitive testing, were related to either verbal or non-verbal cognitive abilities in the study by Hochstenbach et al. (1998). In another study, Madureira and colleagues (2001) found cortical lesions to be more frequent in stroke patients demonstrating any deficits in level of cognitive function.

2.2.5. Personal Characteristics and Post-Stroke Cognitive Function

In addition to the impact of the pathological features of stroke, the cognitive outcome following such an event may also depend on certain personal characteristics of the individual in whom the stroke occurs. The identification of such patient-based factors has been considered important because they indicate that particular traits or health states present before the onset of stroke may affect a patient's susceptibility to cognitive impairment when it eventually takes place (Elkins et al., 2005).

In this context, the patient's age at the time of stroke has been found to influence both the likelihood of cognitive impairment and the degree of recovery following such an event. For example, MMSE-defined cognitive impairment at three months was more frequently observed in older stroke patients in univariate analyses by Patel et al. (2002) and Zhou et al. (2005). However, whereas multivariate effects of age on cognitive impairment were noted by Zhou and colleagues (2005), the former study failed to demonstrate such effects (Patel et al., 2002). Moreover, in a study by Tham et al. (2002), stroke patients showing global cognitive impairment six months post-stroke were found to be significantly older at the time of stroke. When the patients were further divided into those who had remained stable, those who had improved, and those who had deteriorated from the time of baseline testing to one-year follow-up, significant differences in mean age were observed. Higher mean age was also related to less one-year global cognitive recovery in elderly stroke patients in a subsequent study by Patel et al. (2003).

Relatively limited evidence exists on the effects of age at stroke onset on outcomes across specific functions. However, in a study by Madureira et al. (2001), memory-impaired stroke subjects were found to be older at the time of disease-onset than those without memory deficits (62.9 versus 57.8 years, respectively). An identical pattern was observed when patients with any cognitive deficit were compared with cognitively intact subjects. Subsequently, older stroke patients were found to be more impaired in global function (assessed by the CAMCOG), cognitive speed, and memory, six months after the event, whereas no age effects were found on cognitive flexibility (assessed by the Stroop Test and Concept Shifting Task) (Rasquin et al., 2002).

In comparison to the influence of age on subsequent cognitive function in patients with stroke, findings regarding sex differences in post-stroke cognitive performance have been less consistent. As an example, Rasquin et al. (2002) showed that, compared to men, women were significantly more likely to be impaired six months post-stroke in cognitive speed, while no sex differences were observed for either global cognitive function, memory, or cognitive flexibility. Whereas similar null findings with regard to global levels of cognition were also reported by other researchers (Patel et al., 2003; Tham et al., 2002; Zhou et al., 2005), less cognitive recovery over a period of one year was associated with female sex in another study (Patel et al., 2003). However, in a study by Hochstenbach and colleagues (1998), male and female stroke patients were found to perform differently on different cognitive tasks requiring a verbal response; men performed better on visuospatial tasks whereas women did better on tests of memory. In contrast, no gender effects were observed on non-verbal cognitive tasks.

Further to the influence of patients' demographic characteristics, socioeconomic status, education, and medical history, may play a role in modulating the effects of stroke on cognitive outcomes. In the study by Patel et al. (2002), lower socioeconomic status was associated with cognitive impairment at three months post-stroke, and this was further shown by Zhou et al. (2005). Whereas Zhou et al. (2005) and Tham et al. (2002) both noted lower education to be associated with greater global cognitive impairment at three months as well as less one-year recovery, Madureira et al. (2001) had previously found less years of schooling to be more frequent in stroke subjects who either had specific memory deficits, or any cognitive impairment, compared to intact patients. However, these differences failed to reach statistical significance. Earlier, in an investigation by Tatemichi and associates (1994), no effects of either education or race were observed on levels of cognitive impairment three months after stroke.

Similar conflicting evidence has been reported with respect to both medical history and stroke risk factor levels, underscoring the need for additional research. For example, in an early report by Desmond et al. (1996), the presence of diabetes mellitus was significantly associated with a failure to exhibit improvement in global cognitive function. In contrast, no effects of either depression, medication use, or other influences were noted. Importantly, recurrent stroke during follow-up was not associated with cognitive recovery. Similarly, no effects of each of a number of stroke risk factors, such as heart disease, vascular disease, hypertension, smoking, or diabetes, were observed on either verbal or non-verbal cognitive skills by Hochstenbach et al. (1998).

This was, however, not found to be the case in several other studies which demonstrated that, for cognitive outcomes in stroke patients, such risk factors may be of importance. Thus, Madureira et al. (2001) found that, in comparison to stroke patients without memory deficits, those with memory impairment were more likely to consume alcohol. No such effects were, however, found for stroke patients showing any cognitive impairment. Similar effects of alcohol were also found by Zhou et al. (2005), but in addition, stroke subjects who demonstrated global cognitive impairment were also more likely to have had prior stroke and atrial fibrillation (no association with hypertension, diabetes, heart failure, myocardial infarction, or smoking, were observed). In multivariate models, only alcohol consumption was associated with cognitive impairment. Almost identical null-findings with respect to prevalent cardiovascular disease and established risk factors were reported by two other studies (Patel et al., 2002; Patel et al., 2003), whereas in a recent longitudinal investigation by Elkins et al. (2005), involving elderly women in the Study of Osteoporotic Fractures (SOF), pre-existing hypertension was associated with a greater decline in measures of global cognition, executive functioning, and attention, following the onset of incident stroke. These last results suggest that hypertension-induced subclinical brain injury prior to stroke may decrease the brain's ability to adapt or recover from acute ischaemia, thereby increasing susceptibility to cognitive decline. In this context, hypertension-related cerebral damage may act to decrease the brain's functional capacity (the brain's "cognitive reserve" concept maintains there are aspects of brain structure and function that can buffer the effects of neuropathology such that the greater the reserve, the more severe the pathology must be to induce functional impairment) to recover or adapt following the onset of an acute ischaemic episode (Richards and Deary, 2005).

2.2.6. Study Limitations

As is evident from the previous review, the current literature on stroke and cognitive function in old age comprises studies which frequently have generated contradictory findings. Existing investigations vary greatly methodologically and a majority of reports tends to suffer from any of a number of methodological shortcomings regarding the study of the above association. In particular, both the quality and validity of individual reports may be questioned on the basis of how cognitive function has been assessed, the timing of cognitive testing relative to the onset of stroke, the determination of stroke status, the selection of comparison subjects, and handling of potential biases and confounding.

Data on cognitive function have only been collected at a single point in time in most studies. This is an important limitation for three reasons. First, even though cognitive test performance may be a valid endpoint in itself, it constitutes a less direct measure of the pathological process under study which is characterised by change in cognitive function over time. Second, as a result of the first point, performance scores may not be a good indicator of change in cognitive performance over time. Third, a number of factors other than the process under study may influence cognitive test performance at a single point in time. Unless included in the study protocol and measured, the effects of these cannot be accounted for in the analysis. In contrast, only a few studies have provided longitudinal data on cognitive performance over very modest follow-up periods. Moreover, still fewer have collected longitudinal data on specific cognitive functions. Several studies have reported on the proportion of subjects having cognitive impairment at different time-points post-stroke, which on different occasions during follow-up, may in fact comprise different individuals. Much fewer reports have actually examined intra-individual change in cognitive performance over time in subjects with stroke.

Extensive domain-specific data have been gathered in several case-control studies using cognitive test batteries. In comparison, cognitive functions have been less thoroughly examined in population-based investigations. In fact, in several such studies, only global cognitive measures have been administered. This is potentially problematic since the most widely used global tests were not designed to study change in cognitive function. Moreover, global tests may not capture a wide spectrum of cognitive abilities and may suffer from either floor or ceiling effects. Most importantly, global tasks are likely to be insensitive to subtle changes in cognitive performance and mask differences in rates of decline in different cognitive functions.

The length of the time interval from the onset or diagnosis of stroke to the assessment of cognitive function varies considerably across studies. The timing of cognitive assessment may greatly influence the study results. For example, particularly high rates of impairment may be observed where cognitive testing is performed very early following the event, during which time acute confusional or sensorimotor states may influence cognitive test performance.

Standardised diagnostic criteria for stroke, such as that from the WHO, have usually been used despite not always being explicitly stated. In a majority of reports, brain imaging has been available, but in some multi-centre investigations, a single imaging protocol has not always been followed at different study sites. In other contexts, imaging data have not been provided for all subjects, and in the case of negative findings, repeat scanning has not been performed. On the whole, few studies have provided detailed imaging data allowing an analysis of specific stroke characteristics with patterns of cognitive function.

Case-control studies tend to recruit consecutively admitted hospital patients. On several occasions, recruitment has been limited to patients with ischaemic stroke. In other studies, mixed stroke subtypes have been included. It is possible that different stroke types influence cognitive outcomes to a different extent. Moreover, regarding stroke aetiology, different subtypes tend to overlap substantially but not entirely, which may affect the analysis of the relationship with cognitive function. In still other analyses, non-stroke TIA patients have been included, whereas elsewhere these have been deliberately excluded. The result of their inclusion may be dilution of any cognitive effects seen among cases. Recruitment of people with a first-in-a-life-time stroke has been emphasised in some research contexts whereas in others not. It is unclear whether multiple strokes are associated with progressively worse cognitive function.

A major challenge of case-control studies is the selection of suitable stroke-free comparison subjects. In the current literature, a number of different paths have been taken, including the use of published norms, non-stroke community-drawn controls, and patients' spouses. The use of community-based controls has been criticised for 'overmatching' and thus potentially overestimating the cognitive effects of stroke. In addition, a number of biases may be introduced by using healthy population controls in such case-control studies.

A number of potential confounding factors need to be considered in the study of cognitive function in stroke. Sociodemographic factors have usually been taken into account in a majority of studies but other factors less so. A major limitation of most current studies is the inadequate control for confounding by vascular risk factors. In a number of investigations, cases and controls differ significantly on such factors. In particular, hypertension, smoking, diabetes, and atrial fibrillation may independently affect cognitive function. Prior cognitive ability is associated with cardiovascular disease (Hart et al, 2004) and later-life cognitive function (Deary et al, 2000) but has rarely been considered. Few studies have directly estimated peak cognitive levels. Whereas most studies have only used proxy measures, such as level of education or socioeconomic status, residual confounding by prior ability is difficult to rule out in most current reports.

Further to confounding, several other methodological challenges may threaten study validity. In particular, case-control studies tend to be based on small, selected patient samples which may not be representative of other patient populations. Nor may the results from such samples be generalised to stroke survivors in the community. Patient samples are likely to comprise more severe cases that may be difficult to study longitudinally. In a number of studies, follow-up has proved difficult due to high mortality or drop out rates which may jeopardise the validity of the study. In contrast, population studies include elderly survivors of stroke who are likely to have milder stroke pathology. However, the age range of subjects tends to vary widely between studies. Whereas some have focused on the very old, others have been based on much younger samples. Still other reports comprise patient groups whose age range spans several decades. When very old subjects are included, in whom cognitive impairment and decline is most prominent, it is possible that in some patients stroke simply coincides with pre-existing Alzheimer's disease (AD) pathology as an underlying cause of incident cognitive decline: indeed, mixed aetiology for cognitive decline may be common in the oldest subjects. In several investigations the following have been excluded: patients with possible or probable AD, those institutionalised or dependent pre-stroke, those with low cognitive test scores pre-stroke, and those meeting dementia criteria according to proxy. Whereas these approaches are likely to reduce the possibility of unrecognised, concomitant cognitive impairment, they may not exclude it. In comparison, when recruited to research, younger subjects may be more likely to be free of co-existing neurological pathology but stroke events may be few and the outcome under study difficult to detect (although the possibility of reduced cerebral blood flow relating to cognitive decline before the onset of stroke must be considered).

2.2.7. Section Summary

Disruption of normal cognitive processes may be the outcome of atherothrombotic disease that can lead to acute cerebral ischaemia through a number of mechanisms. Over the past decade or so, there has been growth in the number of empirical investigations examining neuropsychological functioning following stroke. In both hospital –and community-based samples, a high frequency of post-stroke cognitive impairment has been reported, the size of which may depend on the time interval from the event onset to the assessment of cognitive function. Indeed, in several studies, an improvement in intellectual functioning has been noted, as evidenced by a reduction over time in the proportion of patients meeting criteria for cognitive impairment. It is possible that various aspects of the acute event itself, such as its type, laterality, and location, or patient characteristics present at the time of the stroke, including the patient's age and medical profile, may influence the extent of recovery in cognitive function following stroke. Further clarification of the role of these in post-stroke mental performance may assist in the identification of stroke patients at particular risk for further cognitive deterioration.

In several investigations, stroke patients have been noted to perform worse on cognitive tests relative to stroke-free controls. For example, there is evidence of involvement of global cognitive ability as indexed by mental status tests, but the administration of detailed neuropsychological batteries to hospital samples has suggested more selective cognitive deficits, specifically on measures of attention and processing speed. Whereas there has been some support from population studies regarding the influence on global measures, findings are conflicting with respect to the specificity of the effects. Additionally, there is an apparent lack of population-based evidence regarding whether stroke may be associated with an increased decline in cognitive function over time. A number of methodological issues are likely to need attention in future studies examining the relationship between stroke and intellectual functioning. Among the important ones are the timing and completeness of the neuropsychological assessment, the selection of cases and controls, and handling of potentially confounding factors.

2.3. COGNITIVE FUNCTION AND CORONARY HEART DISEASE

2.3.1. Introduction

Coronary heart disease is a major cause of death and disability. It is a manifestation of atherosclerosis in the coronary circulation and may be considered as a marker of systemic atherosclerosis. In comparison to other study endpoints, measures of neuropsychological functioning have rarely been the principal outcome in studies of CHD. It is possible that the overall paucity of studies in this area reflects a general lack of appreciation for the systemic nature of the disease. However, as discussed first in the present chapter, a number of mechanisms may lead to cognitive dysfunction in patients with CHD, although in the absence of overt neurological impairment, subtle cognitive deficits may not be expected in individuals suffering predominantly from a disease of the heart. Furthermore, this chapter provides a review of empirical studies examining patterns of cognitive function in patients with CHD, which is followed by a methodological discussion of published reports. For support, a methodological overview of the studies reviewed in this chapter is presented in appendix A-2.

2.3.2. Mechanisms of Neurocognitive Dysfunction and Coronary Heart Disease

Cognitive impairment in atherosclerotic cardiac disease could reasonably be attributed to several different underlying mechanisms. In particular, three major explanations have been proposed (see Vingerhoets, 2001 for review). First, a generalised systemic process may contribute both to the development of cardiac disease as well as to cerebrovascular insufficiency. Indeed, there is ample evidence showing that the development of atherosclerosis in one arterial territory is likely to be but one manifestation of a widespread, systemic disease. Such a generalised pattern of atherosclerosis is further reflected in the fact that either symptomatic or significant but yet clinically unrecognised disease may co-exist within the same individual, and that disease in one arterial bed should prompt investigation of manifestations of disease in others (Phillips, 2001). Evidence of coronary atherosclerosis has been found in up to a third of individuals with carotid artery stenosis (Mathiesen et al., 2001), and is also frequently reported in patients who have had transient ischaemic attacks (TIA) and cerebral stroke (Russell, 1983). Likewise, asymptomatic carotid stenosis may predict cardiac infarctions as well as infarctions in the brain.

Second, whereas TIAs and stroke in older cardiac patients are frequently the result of concomitant intracerebral or carotid atherosclerosis, cardiogenic cerebral emboli also constitute an important cause of acute cerebral ischaemia. Even though these are hard to diagnose with certainty, it is thought that between 15% and 20% of all ischaemic strokes are cardiogenic in nature (Vingerhoets, 2001). A common source for such emboli is a thrombus lodged within the left auricle or on a hypokinetic or aneurysmal endocardium following MI (de Bono, 1983; Nadareishvili et al., 1999). Of the different substrates of cardiogenic brain embolism, non-rheumatic atrial fibrillation may be most commonly encountered, followed by left ventricular mural thrombi in acute MI. Even though findings are conflicting as to whether cardiogenic emboli show lodging preferences, there is evidence to suggest that the middle cerebral artery or its branches are more commonly involved than other supra-aortal circulatory sites (Oder et al, 1991).

Third, cognitive impairment in cardiac disease may result from either acute or chronic hypoxic brain damage due to cardiac failure. In this context, myocardial infarction constitutes an important cause of congestive heart failure, which is associated with reduced cardiac ejection fraction as a consequence of left ventricle dysfunction. As well as predisposing to thromboembolism, cardiac failure may lead to decreased cerebral blood flow (Pullicino and Hart, 2001). The brain, being a highly metabolically active organ, is depended on adequate blood supply. As a result, cerebral blood flow is autoregulated by intracranial mechanisms but if systemic blood pressure levels fall below the autoregulative window, hypoxia may occur (Vingerhoets, 2001). Impaired autoregulation and failing compensatory mechanisms in advanced cardiac disease could lead to chronic hypoxia, potentially impacting normal brain structure and cognitive processes, but both the rapidity and the extent to which cerebral blood flow is reduced is likely to be of importance for the these outcomes.

2.3.3. Frequency of Cognitive Impairment, Patterns of Cognitive Function, and Coronary Heart Disease

Evidence from clinic-based samples

The overall growing interest in the relation of cardiovascular disease with cognitive function has seen a slow but steady accumulation of studies examining patients with coronary artery disease. In early investigations, where the focus had exclusively been on small samples of cardiac patients with advanced disease, researchers had noticed an increased risk of cerebral infarction and haemorrhage (for discussion see Barclay et al., 1988). In many instances, the infarcts were thought not to result from an in situ thrombosis of cerebral arteries but rather from thromboembolism of an extracranial source. Whether patients with cardiac disease also demonstrate poor cognitive function has been somewhat contradictory.

Barclay and colleagues (1988) examined 20 clinically stable cardiac rehabilitation patients aged between 47 and 85 years. Whereas all were considered free of dementia, seven had had an MI while the rest were recovering from various cardiac surgeries. Subjects with previous stroke were excluded. Cognitive deficits in fine motor coordination (Pegboard Test), memory (Mattis Dementia Rating Scale, MMSE, Mental Status Questionnaire), and initiation and perseveration (Mattis Dementia Rating Scale), were observed in 40% to 60% of the sample. Between 10 and 30% of patients had impairment in naming objects (Confrontation naming), psychomotor speed (Digit Symbol Test), abstract reasoning (WAIS similarities), attention (Digit Span Test), and visuospatial ability (WAIS Block Design). However, when the MI and surgical patients were compared on cognitive tests performance, no statistically significant difference in either global or domain-specific functioning was found. Importantly, whereas three patients had unifocal neurocognitve deficits, 15 showed multifocal findings, suggesting multi-domain cognitive impairment in this population. Whereas the authors did not exclude the possibility that the observed cognitive deficits were in some way related to the underlying cardiovascular disease, they emphasised the need for further studies using non-vascular controls as well as the collection of pre-operative cognitive data from surgical samples.

Perhaps partly in response to the above, Selnes et al. (2003) provided further data on the pre-operative cognitive test performance of 140 elderly patients scheduled for coronary artery bypass grafting (CABG). In addition, 92 catheterisation-diagnosed coronary artery disease control subjects, similar in sociodemographic structure to the patient group, also underwent detailed cognitive assessment. When cases and controls were compared at baseline, using measures of attention, language, verbal and visual memory, visuoconstruction, executive function, and psychomotor and motor speed, no statistically significant differences in test scores were found. This may not be surprising given that cases and controls both had advanced cardiovascular disease at the time of cognitive testing, and in fact were not observed to differ with respect to baseline prevalence of hypertension, diabetes, history of MI, TIA, cardiac arrhythmia, or medication use.

Even though the main objective of the last study was to evaluate the effects of cardiac surgery on cognitive processes the authors noted that, in comparison to published norms, not only the cases but the control subjects also performed relatively worse on tests of verbal memory and timed tasks of motor speed and executive function. In investigations where cognitive performance of severe cardiac disease patients has been compared with that of non-vascular controls, similar patterns of cognitive impairment to that above have been observed. For example, Putzke et al. (2000) administered a comprehensive cognitive test battery to a group of 44 cardiac patients with end-stage disease undergoing routine evaluation for heart transplantation. An equal number of subjects recruited from the community, and without self-reported history of CVD and stroke, comprised the control group. Importantly, cases and controls were matched on age, sex, education, and race. The study showed that, in comparison to controls, the transplant candidates displayed a statistically worse performance on tasks of non-verbal reasoning (The Shipley Institute of Living Scale) and timed tests of psychomotor speed and mental flexibility (Trail Making Test). Moreover, cases were significantly slower on timed measures of fine motor-speed and dexterity (Peg Board Test). In contrast, neither immediate nor delayed recall of verbal material (Logical Memory Test) was affected. It is possible that the discrepancy between these results and that reported above by Selnes et al. (2003) may be explained by the use of different tasks used in the measure of verbal memory.

Finally, Moser et al., (1999) studied a group of 93 cardiac rehabilitation patients whose cognitive test performance was compared to 36 age-matched outpatients attending the same medical facility. Around 55% of cases were found to have had MI, 50% had a history of poorly controlled systolic hypertension, and 41% had undergone CABG surgery. Relative to controls, cases obtained lower mean scores on all cognitive tasks in an unadjusted analysis. In particular, measures of verbal learning and recognition (Recognition Memory Test-Words), psychomotor speed (Digit Symbol Test), and executive functions (Category Fluency), were moderately but significantly affected. In contrast, no statistically significant group differences were observed for either the WAIS-similarities subtest or MMSE-estimated levels of global cognitive function. Furthermore, in an analysis involving only the rehabilitation patients, no differences in cognitive function were observed between those with and without prior MI. Overall, however, these findings suggest mild cognitive deficits on several specific cognitive abilities in patients with advanced cardiac disease.

Evidence from population samples

Some of the methodological challenges faced by clinical studies have partly been overcome in investigations based on community-derived samples. In such studies, information on a number of important confounding factors is usually available and selection bias is less likely to distort the results. On several occasions, cognitive assessment has been carried out on large numbers of individuals whereby the cognitive test performance of diseased individuals is compared to that of healthy subjects selected from the same population. In particular, they have provided greater insight into cognitive function in relation to cardiac disease per se as distinct from the potential influences of concomitant morbidity, previous cardiac surgery, or both. Despite such methodological advances, findings from community-based studies have been somewhat contradictory. For example, negative effects of cardiac disease on global cognitive function were observed by Breteler and colleagues (1994) who found ECG-diagnosed MI to be associated with poorer performance on the MMSE, independently of age and education. Despite only modest differences in mean levels, the total distribution of MMSE scores was found to have shifted towards lower values, thus increasing the proportion of participants with scores indicative of cognitive impairment. In the Caerphilly study, elderly stroke-free men with CHD had statistically lower age and social class-adjusted mean scores on two global cognitive measures relative to men without vascular disease (Elwood et al., 2002). Specifically, the presence of CHD was associated with lower MMSE and CAMCOG scores equivalent to that of 13% and 14% of a standard deviation, respectively. Negative effects of similar magnitude were also observed in men diagnosed as having either ECG ischaemia or angina, but previous MI was not related to poorer global performance. Whether these diagnostic categories were mutually exclusive is not clear, however.

In other cross-sectional analyses, an association of cardiac disease with inferior performance on global cognitive tasks has not been supported. For example, Ahto et al. (1999) found no statistically significant association of CHD, defined either as the presence of angina or a previous MI, with MMSE performance in a study of 486 community-resident Finnish elderly persons. However, for both men and women, cases scored slightly lower compared to controls. In another Finnish study involving 629 elderly subjects, no differences in age and sex-adjusted baseline MMSE scores were observed between subjects with and without a history of MI (Tilvis et al., 2004). However, whereas no data were provided on history of MI, heart failure was implicated in a significantly greater five-year decline in global cognitive performance as well as higher mortality rate over the same study period. Petrovitch and associates (1998) also failed to associate previous MI with poorer performance on the CASI instrument after controlling for age and level of formal education in their study of over 3700 Japanese-American men. This null-finding is of interest in the light of the fact that men with previous stroke or history of CABG surgery, overrepresented among those with history of MI, were not excluded from the analysis. Moreover, neither the number of CHD events nor the time between last event and cognitive assessment were found to be related to performance on the CASI. Even though a single explanation is unlikely to exist, differences in study populations, methods of assessment of cardiac disease as well as cognitive function, are likely to contribute to such discrepancies.

Inconsistent findings have also been produced in several population-based studies that have collected longitudinal data on performance on neuropsychological tests. For example, Zhu et al. (1998) provided three-year follow-up data on 924 men and women aged 75 years and older at baseline. Whereas an average yearly decline of 0.4 MMSE points was observed for the sample as a whole, the rate of decline was not found to be associated with either baseline CHD or heart failure. An adjustment for potential confounders did not change the results. However, since relatively milder cases of cardiac disease were included in this study, the authors did not exclude the possibility that more severe forms of cardiac disease could be associated with impaired cognitive function. Using a longer follow-up, Eslinger et al. (2003) followed 287 elderly men participating in the Western Collaborative Group Study for six years. The results showed that approximately 15% of subjects declined by three or more points on the MMSE. In comparison, over 80% did not decline by the same degree. When decliners and non-decliners were compared, no statistically significant differences were observed with respect to the proportion of subjects having a positive history of CHD (based either on medical review showing the presence of angina, MI, or congestive heart failure, or on ECG evidence of coronary heart disease).

Furthermore, Piguet et al. (2003) examined 377 non-demented (baseline MMSE score of >25) community-dwelling subjects aged 75 years and over for a period of six years. Whereas both subjects with and without heart disease at baseline declined over the follow-up period, those with heart disease did not decline at a steeper rate compared to the non-diseased participants. Identical results were found when the analysis was confined to subjects having a baseline MMSE score of less than 25.

In contrast to these findings, Haan et al. (1999) noted an increased seven-year rate of decline in MMSE scores in subjects with either major ECG abnormalities or congestive cardiac failure at baseline. Statistical control was made for both sociodemographic confounders as well as incident stroke.

Information on the relationship of CHD with performance on domain-specific tests has come from several studies. In particular, Elwood and colleagues (2002) found men with any manifestation of CHD to score less on a task of verbal and mathematical reasoning, relative to non-vascular controls. Also, diseased subjects tended to demonstrate slower mental speed, as measured by a choice reaction task. Moreover, a lower verbal and mathematical test score was observed in relation to angina and history of MI, but not ECG-determined ischaemia. Previous MI was also related to significantly slower reaction times. Overall, the presence of disease was associated with negative effects on verbal and mathematical reasoning, equivalent to that ranging from 12 to 21% of a standard deviation, and that of 17 to 21% of a standard deviation for choice reaction time. Similarly, a regression analysis adjusting for age, sex, and socioeconomic status found history of CHD to be predominantly associated with worse performance on measures of executive control functions in a still older sample from the Berlin Aging Study (Verhaeghen et al., 2003). Severe cardiac disease, evident as congestive heart failure, was in addition associated with worse perceptual speed. When added to the same multivariate model, only heart failure, but not CHD, predicted reduced levels of executive control functioning.

Finally, using some of the same cognitive measures as above, Singh-Manoux et al. (2003) demonstrated how different diagnostic indexes of CHD, estimated from several sources, were related to worse cognitive performance in a large sample, comprising subjects of a relatively younger age to that described in the aforementioned investigations. Interestingly, mean scores on tasks assessing both fluid and crystallised functions, as well as some aspects of memory, were significantly lower in those with disease than those without. Specifically, whereas this was the case for both angina and an all-inclusive category CHD, the MI group exhibited more selective difficulties on tests of verbal reasoning, crystallised ability, and some indices of executive control (Semantic Fluency Test), but neither immediate recall of verbal material nor other aspects of executive control functioning (Lexical Fluency Test). This pattern was observed in both men and women. Similar to the Caerphilly study (Elwood et al., 2002), the size of effects of cardiac disease on particular cognitive measures in this study were found to range from 7 to 34% of a standard deviation.

Limited longitudinal data have been collected on performance on specific cognitive tasks in patients with CHD. In fact, two published studies have produced mixed findings as to whether such patients may be relatively more prone to intellectual decline. In the earlier report, which already has been mentioned, Haan et al. (1999) observed a steeper 7-year decline in psychomotor performance, as assessed by the Digit Symbol Test, in the presence of baseline cardiac disease (either major ECG abnormalities or congestive heart failure). In contrast, neither clinically verified baseline CHD nor congestive heart failure were found to be associated with a greater 4-year decline in domain-specific measures of fluid and crystallised intelligence, memory functioning, and executive control functions (Verhaeghen et al., 2003). Although both cases and control subjects demonstrated some decrease in performance levels over the study period, the investigation failed to implicate CHD in later-life cognitive decline.

2.3.4. Study Limitations

Relatively few studies have examined cognitive function in the context of cardiac disease. Apparent conflicting findings from both clinic and community-based investigations are likely to be attributable to any of a number of methodological shortcomings. Moreover, comparing studies is challenging given their methodological heterogeneity.

Similarly with respect to investigations examining post-stroke mental functioning, the majority of cardiac studies have only provided data on cognitive test performance at a single point in time. In fact, very few population studies, and no clinic-based investigations, have collected longitudinal data on cognitive function. The implications of this have already been discussed in the context of stroke. Furthermore, in most of such follow-up studies, cognitive assessment has been based on global cognitive measures, such as the MMSE. As a result, it is currently not known whether cardiac disease is associated with deficits or decline in all cognitive functions, reflecting a generalised pattern of dysfunctioning, or is confined to some functions and not others. In fact, only two studies, which actually produced conflicting findings, have collected longitudinal data on various functions using a battery of cognitive tests.

Current studies tend to differ significantly with respect to the methods and criteria used in determining cardiac disease. The result is that largely non-equal cardiac problems are often being compared. In clinic-based studies, patients with very advanced disease, such as those attending cardiac rehabilitation or undergoing surgery, are often recruited. On a number of occasions, cases are found to comprise patients with mixed cardiac aetiology, suffering from other systemic diseases, or having undergone surgery. In such circumstances, it may be impossible to identify the exact causes responsible for the observed impairment in cognitive function.

Similarly, across population studies based on survivors of cardiac disease, diverse methods have been used for detecting disease. In a few studies, multiple sources, including past medical history and hospital discharge data, have been used in identifying cases. In others, direct assessments have been carried out, using symptom-based questionnaires or ECG. Often, however, the exact diagnostic criteria have not been explicitly stated. The reliance on a single method only, such as ECG, may result in some true cases being classified as not having disease given the relatively low sensitivity of ECG in detecting previous MI. Further to this, most population studies have collected data on cardiac disease at a single point in time (prevalence) rather than over time (incidence). In this context, some asymptomatic cases, for example, could be wrongly considered being free of cardiac disease.

As mentioned above, clinic-based studies tend to include patients with mixed, advanced cardiovascular problems. Even though the majority of patients have significant underlying CHD, this disease heterogeneity makes the study of specific CHD syndromes difficult. On the other hand, most population studies have either relied on a single all-inclusive CHD category or on one prominent manifestation of the disease (for example, MI). Only few studies have cross-sectionally investigated cognitive function in relation to different CHD syndromes. In particular, limited data have been collected from individuals with subjective or mild CHD, such as angina pectoris. No studies to date have examined function-specific change in relation to different CHD syndromes. In addition, it is of note that few studies have adequately taken into account the potential overlap between different CHD syndrome groups or between subjects with other manifestations of atherosclerotic disease. Specifically, the possibility of confounding by previous stroke has not always been sufficiently excluded in investigations of cognitive function in cardiac disease.

A major problem with clinic-based investigations is that, even though data on cognitive function have widely been provided, the aim of these has not been the study of the cognitive effects of CHD per se. As discussed above, this is reflected in the selection of cases but has also affected the choice of controls. In particular, control subjects have frequently been drawn from other clinical populations, including non-surgical vascular populations. In many instances, these also suffered from advanced vascular disease. On other occasions, relatively healthy, community-based volunteers have also been recruited using various methods. It is likely that the choice of controls exerts major influence on any findings reported from such studies. In population investigations, the choice of control subjects has been less of a problem since both cases and controls are drawn from the same population and undergo identical examination procedures. However, on several occasions, these have not been entirely free of clinical vascular disease. This is reflected in the fact that, cases and controls have been found to comprise subjects with and without a particular CHD syndrome, such as MI, rather than the controls being free of any known vascular disease. As discussed in the context of research of post-stroke cognitive function, confounding by vascular risk factors is also likely to be a problem in studies of cardiac disease and cognitive function.

Population studies are relatively few and some have been confined to men or specific ethnic groups. The findings from these may not apply to either women or other populations. To date, the majority of studies has predominantly been cross-sectional and longitudinal reports on cognitive function are still scarce. As a result, little is known about the directionality of the relationship of cardiac disease with cognitive function. Secondary changes due to cognitive impairment and its sequelae may occur that can affect the development of vascular disease. Moreover, a few studies have collected longitudinal data on cognitive change from very old subjects but these may be biased if the subjects with both the exposure and outcome are disproportionately lost to follow-up. For example, true cognitive effects of MI could be missed if individuals with post-MI cognitive impairment died before being cognitively assessed at follow-up.

2.3.5. Section Summary

As is evident from the discussion above, several pathways exist through which patients with clinically overt CHD may be at risk of cognitive impairment. As a marker of atherosclerosis, CHD may be associated with clinically unrecognised cerebrovascular disease. Moreover, atherosclerosis-induced cardiac pathology may predispose to cardiogenic emboli and possibly reduced ventricular function which may lead to a state of either acute or chronic cerebral hypoperfusion. So far, however, this potential source of variance in cognitive ability has generated somewhat limited empirical interest. Even though some early investigations demonstrated both frequent and widespread deficits across mental abilities in samples of cardiac rehabilitation or surgical patients, these studies were limited in several ways. Most importantly, since the findings are generally based on individuals both with highly advanced cardiac disease as well as multiple other illnesses, the value of these studies in shedding light on patterns of cognitive function in relation to CHD may be questioned. In population samples, different indices of CHD have been associated with worse performance on measures of global cognitive ability. In addition, there is limited evidence in support of an effect of CHD on longitudinal decline in general mental ability. Interestingly, however, several population-based studies have failed to confirm the above finding despite potential confounding by either prior ability level or stroke. Possibly, global cognitive measures may not be suitable for capturing subtle cognitive deficits in patients with CHD. The use of neuropsychological tests has provided data that suggest measures of fluid ability, including abstract reasoning, executive function, and information processing speed, may be disproportionately affected in CHD patients. However, longitudinal data on specific cognitive abilities in population samples is both scarce and conflicting, highlighting the need for further research in this area. In particular, additional population-based studies are required for outlining the pattern of change in specific cognitive domains in relation to different CHD syndromes, taking into account potential confounding by co-existing atherosclerotic risk factors.

2.4. COGNITIVE FUNCTION AND ATHEROSCLEROTIC DISEASE

2.4.1. Introduction

The aim of the present section is to provide an overview of current investigations of the neuropsychological profile of patients with atherosclerotic disease of the carotid and lower-extremity arteries, which is followed by a methodological critique of published reports. On the whole, relatively few studies have systematically examined cognitive function as a primary outcome in relation to these manifestations of atherosclerosis despite the considerable burden of morbidity they are associated with. Carotid artery disease constitutes a major risk factor for cerebral ischaemia and the risk of both fatal and non-fatal cardiovascular events is substantially increased in patients with peripheral leg disease. From this perspective, disruption of normal neurocognitive processes might be expected in individuals with generalised atherosclerotic disease. As a result, the potential mechanisms leading to cognitive impairment in these patients will first be described. A methodological summary of the studies reviewed in this chapter is supplied in appendix A-3.

2.4.2. Mechanisms of Neurocognitive Dysfunction and Peripheral Atherosclerotic Disease

As already pointed out, atherosclerosis is a chronic, systemic disease of large and medium-sized arteries. There is widespread agreement that atherosclerosis in the carotid and the lower extremity-arterial tree, represent just one manifestation of similar pathology in other arterial systems (Drouet, 2002). In fact, it has been suggested that the presence of atherosclerotic disease in the periphery should prompt an inquiry into ischaemic manifestations in other major organs in the individual, particularly the brain and the heart (Phillips, 2001).

Whereas severe narrowing of either carotid or cerebral arteries could obstruct blood perfusion to the brain, thereby increasing the possibility of cognitive dysfunctioning, atherosclerosis in the carotid tree is also associated with a substantially elevated risk of acute thromboembolic cerebral events. For each 10% increase in the degree of arterial stenosis, the risk may be increased by as much as 26% (Mathiesen et al., 2001). Depending on their size, shape, and the artery in which they will ultimately lodge, the effects of circulating emboli on neurologic functioning vary widely. Even in the absence of clinical stroke, cerebral microemboli (detected using transcranial Doppler ultrasound) from ulcerous atheromatous lesions in the carotid arteries may frequently be observed over time in most, if not all, patients with significant stenosis (Hutchinson et al., 2002). Whereas it has been hypothesised that large numbers of such clinically silent emboli may potentially lead to progressive cognitive dysfunctioning (Russell, 2002), they also strongly predict both TIAs and ischaemic brain infarction (Molloy and Markus, 1999).

Despite the low prevalence of ultrasound-determined carotid stenosis in the general population, its frequency has been found to rise steeply after 60 years of age (Mathiesen et al., 2001). In populations of patients with signs of atherosclerosis in other arterial beds, including the lower extremities, the prevalence of carotid atherosclerosis is increased several fold (Cheng et al., 1999). Furthermore, angiographically-assessed coronary artery disease may be evident in up to 90% of individuals with symptomatic peripheral arterial disease, while cerebrovascular disease may be present in as many as one half of patients (Vogt et al., 1992). The systemic nature of atherosclerosis is further reflected in the elevated risk individuals with symptomatic arterial narrowing in the lower extremities have of both fatal and non-fatal vascular events (Dormandy and Murray, 1991). Moreover, an association of low ABPI, indicating increased lower-extremity arterial stenosis, with an increased risk of both non-fatal MI and stroke in the general population has been demonstrated (Leng et al., 1996).

2.4.3. Frequency of Cognitive Impairment, Patterns of Cognitive Function, and Carotid Disease

Evidence from clinic-based samples

Few studies have been published on the relationship of carotid atherosclerosis with performance on neuropsychological measures. So far, our knowledge of this association has largely come from small-scale clinical investigations based on patients undergoing carotid endarterectomy (CEA), which now has become a routine surgical procedure for the prevention of cerebrovascular insults in individuals with advanced atherosclerotic disease in the carotid arteries. As the number of patients undergoing such an operation has increased, there has been a growing interest in the effects of CEA on cognitive function. In evaluating the cognitive effects of carotid surgery, studies have normally collected detailed cognitive data both before and after the operation. However, from the pre-operative cognitive performance levels, some insight into the neuropsychological profile of patients with severe carotid atherosclerotic disease may be gained.

In the light of what has already been discussed, it may not be surprising that relative to controls, CEA patients have generally been found to exhibit deficits in multiple cognitive domains. Thus, for example, a sample of 36 CEA patients (mean age 63.3 years) was found to have statistically significantly lower mean scores on tasks (selected to represent both left and right hemispheric functions) assessing auditory information processing (Dichotic Listening), psychomotor speed (Finger Tapping Test), measured reaction and movement times (Motor Planning Test), executive functioning (Verbal Fluency), and visuospatial ability and memory

(Complex Figure Test Copy), compared to age and education-matched norms (Brand et al., 2004). In this study, in which pre-operative cognitive testing was carried out the day before operation, 26 of the 36 patients had more than 75% carotid stenosis as determined by ultrasonography, whereas the rest had unilateral carotid occlusion. Although not accounted for in the analysis, only seven CEA patients were found to be asymptomatic, while 19 had experienced TIA, and 8 had suffered stroke. Moreover, 14 had either hypertension or history of heart disease, and 17 were either current smokers or recent quitters.

Kishikawa et al. (2003) also found lower mean scores on both global cognitive measures (MMSE) and domain-specific tests (Verbal Memory, Benton Visual Retention Test) in 23 elderly CEA patients who were compared to age and education-matched hospital controls without carotid stenosis. Cognitive assessment of cases was performed two weeks prior to surgery. As in the previous study, cases had more often had TIA and stroke as well as higher pre-surgery levels of several cardiovascular risk factors. Moreover, the differences between cases and control were not assessed statistically.

A third study compared the pre-operative cognitive performance of older CEA patients to that of two selected groups of controls (Aharon-Peretz et al. (2003). In contrast to the two previous reports, cases were found to be asymptomatic despite having carotid stenosis of more than 70%. Whereas one group consisted of non-demented volunteers with no evidence of carotid stenosis (n=14), and matched with the patient group on major risk factors, the other control group comprised 24 healthy age and education matched volunteers. When compared to the former control group, few differences in pre-operative performance levels were observed. Cases and controls differed only with respect to attention and mental processing speed (assessed with part A of the Trails Making Test). The patient group neither performed worse on the MMSE nor tasks of immediate and delayed verbal memory. Relative to the healthy group, however, CEA patients had poorer performance on several measures, most notably on those relying on attention, visual searching and processing speed, verbal learning abilities, and other frontal lobe functions. Again, no statistically significant differences were observed in either MMSE scores or in performance on tests of verbal memory.

Findings of no differences in pre-surgery levels of cognitive function between CEA patients and controls have also been reported (Fearn et al., 2003; Iddon et al., 1997). This is surprising given that in both cases, symptomatic CEA patients were compared to non-vascular controls. However, only in the latter report where the differences formally assessed using statistical methods (Iddon et al., 1997). In the former study (Fearn et al., 2003), 159 CEA patients (mean age of 68.0 years) with carotid stenosis of 70% or more, were found to have similar reaction times, attention speed times, levels of accuracy in word and picture recognition, and in memory, as 20 elderly urological surgical control subjects. Although the control subjects were all free of clinical cerebrovascular disease, approximately 65% of the CEA patients had a past history of TIA and 35% had suffered clinical stroke. Earlier, Iddon and colleagues (1997) had failed to observe differences in cognitive performance between 30 elderly CEA patients and controls on a number of neuropsychological measures, indicative of either frontal or temporal lobe damage (e.g. tasks involving spatial recognition, short-term memory for spatial information, pattern-location associations, verbal fluency etc.). The lack of association with pre-operative cognitive performance is of interest given that, among cases, patients with history of TIA were included in the study.

Evidence from population samples

Limited community-based evidence exists of the association between markers of carotid atherosclerosis and global cognitive function. Moreover, with respect to particular cognitive functions, evidence suggests tasks assessing fluid abilities, including attention skills and psychomotor speed, may be disproportionately affected. For example, in an early cross-sectional analysis of the Rotterdam study, a study of 4971 institutionalised and non-institutionalised subjects aged 55 to 94 years, the presence of ultrasonographically-determined internal carotid plaques was associated with a shift in the distribution of MMSE scores towards lower values after potential confounding by age, sex, and education, was taken into account (Breteler et al., 1994). However, whereas the difference in mean scores (0.4 MMSE points) between those with and without plaques was found unlikely to be of clinical importance, the authors emphasised the contribution of atherosclerosis to cognition at the population level. Importantly though, neither confounding by prior stroke nor cardiovascular risk factors was taken into account in the analysis.

Auperin and colleagues (1996) showed subsequently that higher prevalence of carotid plaques was associated with lower MMSE scores in a community sample of stroke-free men, aged 59 to 71 years. This finding was further supported in a multivariate analysis, adjusting for demographic, lifestyle, and some medical variables. Identical patterns were observed for psychomotor speed (Digit Symbol Test), but not for tasks requiring attention, non-verbal reasoning, visuospatial perception, and memory. Furthermore, negligible or non-existent effects of intima-media thickness (IMT) with cognitive function were observed (a weak, inverse relation was found with verbal fluency in men with plaques only). In contrast, carotid disease had no influence on cognitive performance in women.

Some evidence in support of a causal role of carotid disease in cognitive impairment was provided in a recent report from the Cardiovascular Health Study (Johnston et al., 2004). Few studies have attempted to distinguish between the role of carotid stenosis as a marker of underlying systemic disease and vascular risk factors, and its causal role in brain ischaemia. In this inquiry, all subjects with either prevalent or incident stroke, TIA, or history of CEA were excluded. A cross-sectional analysis revealed that, those with high-grade left-sided carotid stenosis ($\geq$75%) had both lower mean modified MMSE (mMMSE) scores and greater global cognitive impairment (an mMMSE score less than 80 out of 100) compared to subjects without left-sided stenosis. Identical findings were observed for psychomotor speed (Digit Symbol Test). However, when five-year decline in cognitive scores was compared in these two groups, only an association with mMMSE scores was noted. A greater annual decline in scores was found in those with high-grade left-sided stenosis relative to the comparison group (-2.12 points per year versus -0.44 points per year). Similarly, 50% of the diseased subjects compared to 19% of controls declined by more the one mMMSE point a year on average. These associations persisted after demographic and vascular risk factors as well as right-sided stenosis where controlled for. Relative to subjects without left-sided stenosis, higher rates of decline were also seen in subjects with milder degrees of the disease (1%-74% stenosis).

In contrast, substantially less, or non-significant, associations were found with either cognitive test when subjects with right-sided stenosis (≥75%) were compared to those free of right-sided stenosis. These results were found to confirm the main study hypothesis which had stated that high-grade stenosis of the left, rather than the right, internal carotid artery would be associated with greater mMMSE deficits and decline, since in right-handed persons this measure primarily tests left hemisphere functions. Moreover, if causal in nature, such an association would persist after adjusting for right-sided stenosis and vascular disease. The authors had also assumed that IMT, rather than being a direct cause of cognitive impairment like carotid stenosis, constituted a marker of generalised atherosclerosis and concomitant risk factors. In this context, relative to subjects in the lowest quartile of IMT, those in the highest quartile had lower global and psychomotor speed test scores at baseline, and steeper five-year decline in mMMSE scores. However, no side-preference of effects was observed. In addition, the associations were greatly attenuated when adjusted for vascular risk factors, thus further supporting the notion of IMT as an indicator of the burden of underlying vascular disease.

So far little is known about the mechanisms behind cognitive impairment in carotid atherosclerotic disease, even though several explanations have been proposed. For example, if causal, the effects of carotid disease could potentially be attributed to clinically silent microembolic infarcts, arising from atherosclerotic lesions. On the other hand, haemodynamic disturbances, resulting from severe carotid stenosis, might also interrupt normal brain and cognitive processes. It is therefore of interest that, in the only population-based investigation to empirically test these hypotheses, neither in fact received empirical support (Mathiesen et al., 2004). In this cross-sectional analysis of elderly stroke-free individuals, subjects with carotid stenosis (≥35%) scored significantly lower on tests of attention and psychomotor speed, sustained attention, memory, and motor functioning. These effects were found to be independent of age, sex, and level of education. When further adjusted for MRI-determined subcortical white matter lesions, and lacunar (lesions 5-15 mm in size) and cortical (lesions >15 mm in size) infarcts, most of the associations still remained. This suggested that the association of carotid disease with cognitive test performance was unlikely to be accounted for by the presence of clinically unrecognised brain infarcts. Interestingly, similar results were found when the analysis was limited to subjects without any visible structural MRI lesions. Furthermore, the authors considered cerebral hypoperfusion to be an unlikely explanation since the majority of carotid patients had relatively low-grade stenosis. Therefore, they postulated that carotid disease, rather than being a direct cause of cognitive impairment, constituted a marker of either intracerebral or systemic atherosclerosis, an explanation that Johnston et al. (2004) had refuted in their study.

2.4.4. Frequency of Cognitive Impairment, Patterns of Cognitive Function, and Peripheral Arterial Disease

Evidence from clinic-based samples

As in carotid disease, patients suffering from atherosclerotic narrowing of the arteries in the legs tend to have high levels of cardiovascular risk factors and may be at an increased risk of cerebrovascular disease. Whether cognitive function is also affected in such patients has only been investigated in a limited number of studies. Moreover, a further limitation of some of the earlier studies was reflected in the fact that these were not designed to evaluate the relationship of lower extremity atherosclerosis with cognitive function. Nevertheless, some insight into the extent of cognitive impairment in such patient samples can be gained from these reports. For example, in a sample of 60 leg amputees undergoing evaluation for prosthetic limb fitting and rehabilitation, 10% were found to have severe deficits in multiple cognitive domains, including memory, orientation, and attention and concentration (Pinzur et al., 1986). This impairment was considered severe enough to limit the patients' capacity to learn to use a prosthetic limb successfully. The study, which was restricted to male patients (some as young as 34 years of age), was found to be methodologically limited in several ways. Apart from not using a control group, the patient sample included subjects of different aetiological backgrounds. Thus, even though the majority of amputees had peripheral vascular insufficiency, six subjects had been amputated as a result of trauma or other reasons. Moreover, not all patients received the same set of cognitive function tests, and whereas those below 60 years of age were administered the WAIS instrument, older subjects were tested using the Test of Mental Functions for the Elderly, the Auditory Verbal Learning Task, and the Rey's Complex Figure Task. Unfortunately, since no data on actual test outcomes were provided in the report, no firm conclusions about the level of cognitive performance can be drawn from this study.

In a second report, where the aim was to investigate neuropsychological functioning following major surgery in 312 CABG electives, a sample of 50 PAD surgical candidates was included as a control group (Shaw et al., 1987). When compared on a standard cognitive test battery, comprising the Trail Making Test B and the WAIS-subtests, no differences in mean pre-surgery test scores were observed between the two groups. Although the PAD group was older and included relatively more women, as expected, the CABG patients showed greater prevalence of pre-operative coronary heart disease. Moreover, the proportion of cases and controls with hypertension, diabetes, previous TIA, or clinical stroke, did not differ significantly but the PAD patients had more evidence of carotid arterial disease. Whilst not confirming the intactness of mental processes, these results rather suggest that the level of cognitive impairment of patients with peripheral arterial disease may be at a par with that in individuals showing advanced atherosclerotic disease in the coronary circulation.

The purpose of the publication of two more recent clinic-based studies was partly to address two major limitations with respect to the investigation of cognitive function in PAD patients; firstly to add to the almost non-existing literature in this area of research, and second; to improve the methodological quality of existing studies. In the former investigation, Phillips et al. (1993) administered a comprehensive cognitive test battery to 14 stroke-free PAD amputees, recruited from a rehabilitation centre, and 14 community-drawn control subjects. Whereas only slight groups differences were found regarding age at cognitive testing (mean age 69.9 versus 67.4 years), the patients were more likely to smoke, have diabetes, suffer from hypertension, and be obese, relative to controls. This observation is likely to influence any conclusions drawn from the study, particularly in the light of the fact that these differences were not statistically controlled for when the groups were compared on tests of cognitive function. As expected, the comparison showed that the amputees scored significantly worse on measures of psychomotor speed (Digit Symbol Test) and problem solving and abstract reasoning (the Modified Card Sorting Test). Moreover, there were trends towards worse performance on measures of verbal fluency, concentration, and visuoperceptual skills. In their discussion, the authors attributed this pattern of dysfunction to concomitant yet clinically unrecognised cerebrovascular disease in the PAD patients. However, as a result of the analytical approach used, the associations with cognitive function could equally have been accounted for by the presence of vascular risk factors, such as high blood pressure or diabetes.

The methodological weaknesses of this former study were partly addressed in a subsequent investigation by Phillips and Mate-Kole (1997). Here, the authors compared cognitive performance across three study groups: a patient group which included both PAD amputees (n=13) and non-amputees (n=16), an atherothrombotic stroke control group (n=29), and 30 community controls. Both control groups were matched with PAD patients on age and education. By employing two control groups, the authors set out to determine whether PAD patients would perform cognitively worse than healthy controls, and moreover, if the pattern of cognitive deficits observed in such patients would be similar to that seen in clinical stroke. The results from the comparison to the healthy controls were in support of the study hypothesis. In fact, PAD patients performed significantly worse on tasks of attention and psychomotor speed, executive function, visuospatial ability, and visual memory. In contrast, no differences were found on tests of language ability or verbal memory.

Furthermore, compared to stroke subjects, PAD patients showed very similar patterns of deficits across cognitive domains, but of less severity. In fact, the performance of the two groups was comparable on six out of the eight cognitive tests used in the study. Also, when the analysis was restricted to the PAD sample, only PAD clinical severity and history of ischaemic heart disease were found as predictors of cognitive dysfunction in a multivariate model. In contrast, none of the conventional atherosclerotic risk factors that were measured exerted independent effects on cognitive outcomes once disease severity was included. Although type 2 statistical error can not be ruled out as an explanation for the null findings, the study provides further cross-sectional data in support of the presence of widespread cognitive deficits in patients with PAD. In addition, it suggests that, in such patients, the cognitive effects of various vascular risk factors may be mediated through the role of the former in the development of generalised atherosclerotic vascular disease.

Evidence from population samples

In several community-based investigations, the presence of atherosclerosis has been determined from clinical symptoms of arterial narrowing in the legs (intermittent claudication). In other contexts, the ABPI has been directly measured and used to indicate arterial stenosis. In relation to the former, Tilvis et al. (2004) found elderly claudicants in the Helsinki Aging Study to perform significantly worse on the MMSE at baseline compared to subjects without intermittent claudication. However, even though the analysis adjusted for baseline age and level of education, it neither controlled for concomitant stroke nor other vascular disease and risk factors. Moreover, intermittent claudication was related to an increased risk (RR=2.2, 95%CI=1.4-3.2) of cognitive decline during the first follow-up year, whereby decline was defined as either an increase in Clinical Dementia Rating (CDR) class or at least a four-point decrease in MMSE score. On the other hand, baseline PAD was not found to be associated with greater risk of cognitive decline at five-year follow-up, but a significant relation with longitudinal mortality was observed. Thus, the lack of association with long-term cognitive decline in this study could have occurred because of selective mortality among PAD patients over the study period.

Similarly, no significant differences were found between subjects with and without claudication at baseline with regard to the rate of decline in MMSE performance over a six-year follow-up in the Sydney Older Persons Study (Piguet et al., 2003). Whereas these findings were based on individuals scoring at least 25 or more on the MMSE at baseline, identical results were noted when the analysis was restricted to subjects having a baseline score of less than 25. In response to these results, the authors pointed out that the role of PAD was possibly to increase the risk of mortality early in life, but in older survivors, atherosclerotic disease might have no, or only limited, specific contribution to cognitive decline.

The use of domain-specific cognitive tests in population studies has contributed further to the study of cognitive function in systemic atherosclerotic disease by providing domain-specific information. However, so far findings have been somewhat conflicting. For example, both stroke-free men and women (aged 46-68 years) with intermittent claudication were found to perform significantly more poorly when administered cognitive function tests for the first time 11 years post-baseline by Singh-Manoux et al. (2003). In men with symptomatic PAD, tasks assessing short-term memory, verbal and mathematical reasoning, word recognition and knowledge, and executive function, were particularly affected. When expressed as a proportion of the standard deviation for individual tests, effect sizes ranged from 0.17 (knowledge and recognition) to 0.65 (semantic fluency test). Whereas no effects on either short-term memory or semantic fluency were observed in women with PAD, relative to men, weaker effects were seen on lexical fluency (0.11% of a standard deviation) but stronger on measures of knowledge and word recognition (0.33% of a standard deviation).

In contrast, Elwood and colleagues (2002) failed to show significant effects of intermittent claudication on cognitive test scores in another cross-sectional report based on elderly stroke-free men in the Caerphilly study. However, since diseased subjects were found to obtain lower scores on measures of mental speed, global functioning, and non-verbal and verbal reasoning, the null findings may simply be attributed to a lack of statistical power given that men with peripheral vascular disease were relatively few (n ranged from 31 to 38 depending on cognitive outcome).

Limited longitudinal data still exist on change in specific cognitive functions over time in patients with symptomatic PAD, highlighting the need for further longitudinal investigations in this area. Similarly, longitudinal research of the association of APBI and domain-specific cognitive decline is greatly lacking. This would constitute a valuable addition to the current cross-sectional findings which point to an inverse association between APBI and cognitive performance. In an early study by Breteler et al. (1994), the presence of a low APBI (less than 0.9) was associated with moderately lower MMSE scores, and a shift in the total distribution of MMSE scores, independent of the effects of age and education. Moreover, a low baseline APBI was associated with a steeper decline in MMSE scores over a follow-up period of seven years in a longitudinal study by Haan et al. (1999). These effects were found to be independently of potential confounding by sociodemographic factors and incident stroke. More recently, Price and colleagues (2006) analysed data from 717 older men and women in the Edinburgh Artery Study. The ABPI was measured at baseline and a battery of cognitive tests was administered after 10-years of follow-up. In an age and sex-adjusted model, significant, but modest, positive associations of ABPI were found with scores on measures of non-verbal intelligence (Raven's Progressive Matrices), executive function (Lexical Verbal Fluency Test), and information processing speed (Digit Symbol Test). Although it was not reported whether estimated pre-morbid ability (National Adult Reading Test) was associated with each cognitive outcome, when further controlled for, all associations apart from that with the Digit Symbol Test were attenuated beyond statistical significance. Despite its cross-sectional nature, the authors did not exclude the possibility that atherosclerotic disease in the lower extremities might be associated with steeper decline in cognitive function over time. Clearly, further research is needed to establish such a relationship, and also with other cognitive abilities.

2.4.5. Study Limitations

Similar to that of stroke and CHD, studies of cognitive function in either carotid atherosclerosis or PAD are limited in number as well methodologically. So far, most have been cross-sectional in nature and longitudinal cognitive data have rarely been collected. Moreover, longitudinal data on different cognitive functions are greatly lacking. In fact, some areas of investigation, such as the study of change in different cognitive functions in PAD patients, have been more or less unexplored.

Clinic-based studies of carotid disease tend to be based on highly-diseased individuals, normally undergoing CEA. As with other vascular patients, extensive co-existing disease may be present. These studies have provided some insight into cognitive function in carotid disease even though the aim has been to estimate the effects of surgery rather than atherosclerosis per se on cognition. Regarding lower-extremity disease, some clinic-based studies have included leg amputees, who are unlikely to be representative of the general PAD population. On occasions, cases have been heterogeneous with respect to the underlying aetiology. In other circumstances, PAD patients have been recruited as controls. In several population investigations, PAD has been determined on a single occasion using questions concerning the presence of disease symptoms. As a result, it is possible that some true cases may go unnoticed because of remission of symptoms due to formation of a collateral circulation. Moreover, the use of standard instruments in detecting disease symptoms has not always been ensured.

Confounding by concomitant vascular risk factors as well as other confounders is a major general shortcoming of the studies reviewed above. In particular, disease categories have been found to be non-mutually exclusive of other manifestations of atherosclerotic disease, including stroke. Only on rare occasions have control subjects been free of any clinical cardiovascular disease. In population studies, inadequate control for confounding is reflected in part in the limited use of multivariate statistical methods across studies. Specifically, few attempts have been made to examine cognitive function in lower-extremity atherosclerosis independent of vascular risk factors.

2.4.6. Section Summary

The current literature of the relationship between peripheral markers of atherosclerosis and cognitive function has until now been based on a relatively limited and often contradicting body of evidence. So far, most studies have focused on symptomatic and sub-clinical disease in two arterial beds in particular: the carotid system and in the lower extremities. There is ample evidence showing that atherosclerotic lesions of the carotid arteries constitute an important source of cerebral emboli. Many may be clinically silent. Similarly, individuals with leg disease are likely to have significant changes in other arterial beds and are at an increased risk of major vascular events. Concomitant, yet asymptomatic, cerebral and carotid atherosclerosis may be frequent in such individuals, predisposing them to brain ischaemia and possibly cognitive impairment.

Based on the findings from a few clinical studies, carotid surgical candidates are found to show generalised cognitive impairment relative to controls. Some data in support of this have come from population cohorts but there is also a lack of evidence for such as association. Other reports have found effects on a more restricted set of functions. Clinic-based investigations of patients with leg disease have been few and most of the early studies were often not designed to study cognitive function in relation to PAD per se. Subsequent studies which have been carried out have demonstrated intellectual deficits at a comparable level to that seen following stroke. These studies have, however, been limited in number and based on selected patient samples. Confounding by co-existing atherosclerotic risk factors has also precluded an evaluation of the independent effects of atherosclerotic disease on aspects of cognitive function. Rather than relying solely on global tasks, the use of neuropsychological tests in population samples has provided insights into the pattern of cognitive dysfunction in patients with symptomatic and asymptomatic PAD. However, whereas cross-sectional data are abundant, so far there is a noticeable lack of data linking atherosclerotic disease to change in domain-specific cognitive abilities over time, independently of atherosclerotic risk factors and prior to clinical cerebrovascular disease.

2.5. ATHEROSCLEROTIC RISK FACTORS AND COGNITIVE FUNCTION

2.5.1. Introduction

The prevalence of established risk factors for atherosclerotic vascular disease increases with age in the general population. Specifically, a significant proportion of the risk for stroke and CVDs can be attributed to factors such as high blood pressure, smoking, diabetes, and abnormal circulating lipids. Over the past decades, there has been intense interest in the epidemiological association of these risk factors with both levels of normal neuropsychological functioning and cognitive impairment, not least because of the possibility that these may be amenable to treatment or prevention.

Furthermore, the contribution of other more recently investigated vascular risk factors to adult cognitive function is being examined in a growing number of reports. A major objective of the current chapter is to present findings from published epidemiological studies of the relation of established and novel atherosclerotic risk factors with neuropsychological function. Secondly, wherever possible, a reflection on the potential mechanisms through which these factors may exert influence on normal cognitive processes is provided.

2.5.2. Non-Modifiable Risk Factors

Age

As suggested elsewhere in the text, the cognitive changes observed in normal ageing may be substantial and have attracted much attention. Data on the relation of chronological age and cognitive function in elderly cohorts have been provided by a number of recent, population-based, epidemiological studies (Anonymous, 1998; Brayne et al., 1995; Comijs et al., 2004; Starr et al., 1997). In cross-sectional analyses, an inverse relation between scores on measures of global cognitive ability, such as the MMSE, and age tends to be noted (Brayne et al., 1995; Anonymous, 1998). Higher age has moreover been associated with a downward shift in the distribution of MMSE scores (Anonymous, 1998). Similar findings have been reported in longitudinal studies which have examined change in cognitive function over time. In the Hughes Hall Project for Later Life, a Cambridge-based dementia prevalence study of individuals aged 75 years and older, the oldest age group (subjects 90 years and older) declined by 3.0 points on the MMSE over a period of two and a half years compared to that of 0.9 points in subjects aged 75 to 79 years (Brayne et al., 1995). Furthermore, by using various MMSE cut-off points in order to assess the two and a half-year incidence of cognitive impairment, similar patterns were found, with an increase in new impairment at each age level in the study population irrespective of the cut-off point chosen.

Further recent data came from the Longitudinal Aging Study Amsterdam which found the risk of progressive cognitive decline on the MMSE over a period of six years to be strongly but inversely related to baseline age (Comijs et al., 2004). An administration of a cognitive test battery in the Massachusetts Male Aging Study further demonstrated an inverse, linear association between chronological age and performance on measures of working memory, speed and attention, and spatial relations, in 981 middle-aged to older men (Fonda et al., 2005). Moreover, in a study of 102 high-functioning professional men and women, notable age differences were observed on a number of different cognitive tasks after differences in level of education were controlled for (Compton et al., 2000). Thus, for example, older subjects tended to perform relatively poorly on the Digit Symbol and the Trails A and B tests. In contrast, older subjects obtained higher scores on the WAIS-R subtest of similarities.

These findings, and those of numerous other studies (Gregoire and Van der Linden, 1997; Schaie, 1996), lend further support to the well-known pattern of differential effects seen in cognitive ageing, whereby tasks of crystallised functions seem quite resistant to the ageing process, while those acquired as a result of genetic factors (fluid abilities) may be particularly vulnerable (Compton et al., 2000; Deary and Batty, in press). Despite the correlation with age, however, it is still open to debate whether the observed patterns of cognitive decline occur as a result of ageing per se, stem from the effects of concomitant age-associated pathologies, or both (Hedden and Gabrieli, 2004; Starr et al., 1997). Whereas it has been proposed that specific developmental changes in neural structure and function may underlie age-associated cognitive decline (Bartzokis, 2004; Hedden and Gabrieli, 2004), the incidence of diseases with long and progressive preclinical phases also rises with age. Failure to adequately control for such age-associated pathologies, which are likely to affect cognitive function even at subclinical levels, can falsely lead to the assumption that the ageing process itself is the underlying cause of the observed cognitive decline. In particular, this may pose as major challenge when investigating cognitive processes in old age.

Sex

The hypothesis of sex differences in later-life cognitive function has been investigated in a series of recent population-based epidemiological studies. A general lack of studies in this area has, however, been noted (Barrett-Connor and Kritz-Silverstein, 1999), and somewhat conflicting findings exist. In particular, cross-sectional studies have reported mixed results regarding sex differences in cognitive performance of older people. For example, men were found to obtain higher mean MMSE scores at baseline in both the Hughes Hall Project for Later Life (Brayne et al., 1995) and the MRC CFA Study (Anonymous, 1998). In contrast, no sex differences were observed in general ability as indexed by either the sum of the WAIS-R subtests (Portin et al., 1995) or the CAMCOG instrument (Cullum et al., 2000).

Even though inherent weaknesses in the cross-sectional study design have been mentioned as possible explanations for these null findings, similar contradictory findings have also been noted in longitudinal studies. As an example, in addition to having a higher mean MMSE score at baseline, male subjects in the Hughes Hall Project for Later Life further experienced less (1.56 points) 2.5-year decline in mental status (adjusted for age and baseline performance) compared to women (2.19 points) (Brayne et al., 1995). These findings were, however, not replicated in two recent studies of longer follow-up periods, applying either the MMSE (Comijs et al., 2004) or a measure of global cognitive function based on 19 different cognitive tests (Barnes et al., 2003). Moreover, there is no indication that men and women perform differently at different ages in old age.

Some evidence in support of sex effects on cognitive function in elderly persons comes from studies that have administered neuropsychological test batteries. In sum, cross-sectional analyses have suggested that women may outperform men on memory (Aartsen et al., 2004; Barrett-Connor and Kritz-Silverstein, 1999; Portin et al., 1995) and vocabulary tasks (Barrett-Connor and Kritz-Silverstein, 1999). In a Finnish study, elderly women performed better than men on tests of visuomotor and reciting speed and verbal and object memory (Portin et al., 1995). In contrast, men scored higher on measures of visuospatial speed and visuoconstructive performance.

Whereas more recent (Aartsen et al., 2004; van Exel et al., 2001) cross-sectional work has further replicated the above pattern, results from longitudinal analyses have been less suggestive. For example, no sex differences in 4-year risk of decline on any of the eight CAMCOG subscales in the CC75C study were noted (Cullum et al., 2000). Neither were there any differences between men and women with regard to the rate of decline on several measures of speeded tasks over a period of six years in the Longitudinal Aging Study Amsterdam (Aartsen et al., 2004).

Several explanations have been proposed in order to account for sex differences in cognitive function in old people, among them male-female differences in brain reserve (van Exel et al., 2001) and differential susceptibility to normal or pathological age-associated changes (Barrett-Connor and Kritz-Silverstein, 1999; van Exel et al., 2001). Based on the current evidence, however, it is clear that more work is needed in order to verify the similarities and differences in cognitive function between men and women. That work would begin by properly addressing the methodological limitations of existing studies, such as excluding potential confounding by diverse health and lifestyle factors, before moving on to speculations about causal mechanisms.

2.5.3. Major Modifiable Risk Factors

Blood Pressure

One of the most studied risk factors for cognitive decline is high blood pressure. Blood pressure is easily measured, potentially modifiable, and a strong predictor of cerebrovascular disease. As a result, it has been a candidate variable in a number of epidemiological studies probing into the aetiology of individual differences in cognitive function in later life. So far, however, somewhat mixed results have been produced. In an early study carried out on 202 non-institutionalised subjects aged 60-79 years at baseline, Wilkie and Eisdorfer (1971) examined the relationship of diastolic blood pressure (DBP) with WAIS scale scores at baseline and 10 years later. The results showed that hypertensives (DBP >105 mmHg) had a lower WAIS score than either normotensives or borderline subjects (DBP 96-105 mmHg). Also, over the 10-year follow-up, only the hypertensive group declined in the full WAIS scale score. These findings were only seen in those aged 60-69 years at baseline as opposed to 70-79 years old subjects, none of whom classified as having hypertension at baseline returned for post-testing. When the data were pooled, DBP was negatively related to the majority of WAIS verbal and performance scale sub-tests at follow-up in the younger age-band only. Importantly, even though subjects with a history of cerebrovascular disease were excluded, the study was based on few subjects who might or might not have been treated with antihypertensive agents.

Confounding by medication was taken into account in two subsequent cross-sectional analyses based on the Framingham (Farmer et al., 1987) and the East Boston Study (Scherr et al., 1991) cohorts. In short, both studies failed to find any convincing evidence of a relationship, in either direction, between systolic blood pressure (SBP) and DBP, when determined on a single occasion in old age, and performance on a series of cognitive tests. Excluding those taking antihypertensives was not found to alter the results (Farmer et al., 1987). Moreover, in a third study (Herbert et al., 2004), largely composed of older African-Americans who have been found to be at an increased risk of hypertension, no relation of either SBP or DBP with 6-year change in MMSE scores was noted. Approximately 50% of study participants were receiving antihypertensive medication. While the exact reasons for these null findings remain speculative, it has been argued, that in older cohorts, other pathological factors than blood pressure may be operating concomitantly to compromise mental processes (Wilkie and Eisdorfer, 1971).

The timing of blood pressure measurement relative to the cognitive assessment may therefore prove to be fundamental to the investigation of this association. Moreover, nowadays it can be anticipated that a substantial proportion of elderly individuals may be receiving treatment for hypertension. It is, however, unclear how accurately the measured blood pressure values in these elderly actually reflect long-term exposure levels (Herbert et al., 2004). These problems have been dealt with in a series of large-scale epidemiological studies where cognitive tests were administered to untreated hypertensive patients, and test scores were related to blood pressure levels determined in mid-life. In the Framingham Study, blood pressure values were averaged over five biennial examinations during the period

1956-1964 when few hypertensive participants received antihypertensive treatment (Elias et al., 1993). With cognitive function assessed 12 to 14 years later, the results for the total sample showed a negative, linear relationship between both SBP and DBP and performance on a global composite score as well as on several WAIS subtests (the Logical Memory immediate and delayed recall, the Visual Reproductions, and the Digits Backward). Specifically, every 10 mmHg increase in blood pressure was associated with a decline of 0.04 to 0.07 standard deviations in the composite score. Identical results were obtained in sub-analyses of participants who were untreated at the time of blood pressure measurement or throughout the entire study period.

Subsequent studies using data from midlife blood pressure assessments have reported similar findings. For example, an analysis based on old Japanese-American men in the Honolulu-Asia Aging Study observed a nine percent increase in risk of poor cognitive function (a CASI score of <82) for every 10 mmHg increase in SBP levels determined approximately 25 years earlier (Launer et al., 1995). Another study, involving 999 elderly Swedish men, linked cognitive performance at age 70 to blood pressure levels assessed 20 years earlier (Kilander et al., 1998). Levels of DBP, rather than SBP, were found to be inversely associated with composite test scores obtained in old age. Stronger associations were observed in men who, at the time of blood pressure assessment, were not taking antihypertensive medication. In contrast, another population-based study failed to find evidence of an association between either SBP or DBP (assessed either at baseline or nine years before cognitive testing) and scores on two brief, global cognitive measures (Glynn et al., 1999).

Collectively, the pattern of findings from the studies described above suggests, that whereas blood pressure in old age may contribute relatively weakly to cognitive impairment over and above that of other morbidity, midlife levels short of hypertension may result in trajectories which, lasting throughout the adult life, may contribute to individual differences in cognitive function in late adulthood (Swan et al., 1998).On the other hand, evidence shows that the association between blood pressure and cognitive function in old age may be to some extent be accounted for by individual differences in childhood mental ability (Starr et al, 2004), which needs to be acknowledged as a potential confounding factor in such studies.

Blood Lipids

The current literature of the relationship between blood lipid levels and neuropsychological function has been limited to relatively few reports. Based on these studies, results have been mixed as to whether blood lipid concentrations are positively, negatively, or indeed at all, associated with adult cognition. As early as in 1963, beneficial effects on cognitive performance were demonstrated by actively lowering the level of total serum cholesterol (TC) in 174 healthy, male management and scientific employees (Reitan and Shipley, 1963). Of particular interest was the finding that, in comparison to men (above 40 years of age) who did not experience a reduction in TC levels by either sitosterols or diet, those whose TC concentration was decreased by at least 10% had better cognitive scores on problem-solving and reasoning tasks after 12 months of follow-up. Unfortunately, however, the validity of these results may be questioned given that treatment was not randomised, the comparison groups differed in baseline TC levels, and blinding with respect to treatment was not applied (Muldoon et al., 1997).

Subsequent clinical trials have not corroborated the early results reported above. For example, in the Cholesterol Reduction in Seniors Program (CRISP), a small-scale trial of elderly men and women with elevated LDL-cholesterol levels who were randomised to lovastatin treatment, no differences in Digit Symbol scores were found between two treatment groups and a placebo group after six months of follow-up (Santanello et al., 1997). This was despite large reductions in TC and LDL levels in both treatment groups. In another recent randomised clinical trial involving young to middle-aged adults, a battery of cognitive tests was administered in order to assess patients' tolerance of lipid-lowering treatment (Muldoon et al., 2000). The results from this trial showed an improvement in memory performance over a six-month follow-up among subjects in the treatment arm. Similarly, the placebo group's performance on several cognitive measures, such as on tasks of attention and psychomotor speed, also improved significantly over the same period. Despite being 'gold standard', it is possible that the small samples and short follow-ups of these trials contributed to these somewhat disappointing results.

In a similar manner, an even larger body of observational data has neither been able to shed light on the direction of the blood lipid-cognition relationship in any consistent way. In fact, any meaningful synthesis of the literature has proved to be difficult due to vast methodological differences across studies. For example, a positive association was reported between TC levels and both P300 latency (Wada et al., 1997) and steeper 3-year decline in MMSE scores (Wada et al., 1997) in two small-scale studies on Japanese elderly. Similar findings came from a recent analysis based on the Framingham cohort (Elias et al., 2005), in which multiple measures of TC were used and cognitive function was assessed on a single occasion. In comparison to subjects with high (>240 mm/dL) and borderline-high (200-239 mg/dL) TC concentrations, subjects with low or 'desirable' values (<200 mg/dL) scored lower on the WAIS similarities test, and tasks based on word fluency and attention. In contrast, however, no relationship was noted between TC levels and cognitive performance in Leiden 85+ data (van Exel et al., 2002), although low high-density lipoprotein (HDL) levels were associated with poorer mental status scores (but unlikely of clinical relevance). Neither LDL-cholesterol nor triglyceride levels were related to cognitive function. Still further, two other population-based studies also failed to demonstrate a relationship between blood lipid parameters and scores on several neuropsychological tests (Reitz et al., 2005; Sarti et al., 2001).

Despite the inconsistency in epidemiological findings, a positive association between blood lipids and intellectual functioning may have biologic plausibility. For instance, the brain has a high lipid content, and low circulating lipid levels, perhaps resulting from chronic morbidity and/or poor nutrition intake or absorption in old age, may directly affect neuronal metabolism, neurotransmitter synthesis, and cognitive processes. In the light of this possibility, it is intriguing to consider the findings from two studies demonstrating a negative association between blood lipid concentrations and cognition. In the earlier report, Yaffe et al. (2002) examined the development of blood lipid levels over a 4-year period in more than 1000 postmenopausal women with CHD who participated in the Heart and Estrogen/progestin Replacement Study. Administering the MMSE at the end of the follow-up, the investigators first showed that higher levels of TC and LDL, but neither HDL nor triglycerides, were associated with lower MMSE scores and increased odds of impairment (more than 1.5 SD below the cohort mean). Moreover, reductions in both TC and LDL over the 4-year period were associated with better MMSE scores and lower odds of impairment. In addition, statin use, although not randomised, was also associated with better cognitive performance. Beneficial effects of statin use on IQ change from childhood to old age in dementia-free older survivors of the Scottish Mental Health Survey were also noted by Starr et al (2004).

In the latter of the two investigations mentioned above, an inverse relationship between performance on different cognitive task and serum levels of various precursors and metabolites of cholesterol metabolism was observed, even though no relation with TC was found (Teunissen et al., 2003). In this analysis based on data from the Maastricht Aging Study cohort, higher concentrations of lanosterol and lathosterol, which may be suggestive of greater rates of cholesterol synthesis, were related to poorer performance on verbal learning and memory tasks, independently of age, sex, and education. Whereas not examined in these investigations, it is possible that the inverse relationship of blood lipid levels with cognitive outcomes may be fully or partly mediated through atherosclerosis-based co-morbidity.

Smoking

Smoking is a major modifiable risk factor for vascular and pulmonary diseases, and there has been interest in the possibility that smoking may be associated with poor cognitive function. So far, however, findings have been inconclusive (Elwood et al., 1999; Richards et al., 2003). Results from the population-based Zutphen study of elderly men demonstrated 20% more errors on the MMSE in current smokers compared to never-smokers (Launer et al., 1996). Level of disagreement between current smoking status and reported smoking history five years earlier was assessed, and found to be independent of cognitive function and disease. However, in a subsequent report based on the Caerphilly cohort (Elwood et al., 1999), no differences in MMSE performance were observed between current and never-smokers. Whereas not assessed in the former study, no clear evidence of an association between the amount and duration smoked and cognitive test performance was found in the latter investigation. Such a null result had also been reported earlier by Galanis and colleagues (1997) who examined performance on global cognitive tasks in relation to pack-years of smoking in elderly Japanese-American men. In all the studies, smoking was assessed by self-report which may invite recall bias to the data. Even though smoking status may be relatively well reported, self-report of exposure levels by older people may be influenced by cognitive status at the time of assessment (Woodward, 2002).

The above issues have partly been addressed in other studies. For example, in one recent investigation, 9209 participants aged 65 years and older were followed over a mean period of 2.3 years (Ott et al., 2004). Administering the MMSE, the study showed that both male and female current smokers declined at a greater rate compared to those who had never smoked. In addition, a weak but statistically significant inverse relationship was found between the rate of cognitive decline and the number of pack-years of smoking, thereby providing further evidence of a deleterious influence of smoking on cognitive processes in older people. However, whereas potential confounding by any of a number of disease and psychological factors could have accounted for these findings, this was unlikely to be the case in an earlier analysis based on the British 1946 birth cohort study (Richards et al., 2003). Adjusting for a range of possible confounders, among them an estimate of early-life cognitive ability, the investigators studied change in cognitive functions from age 43 to 53 in both men and women. Despite the young age of the sample, a significant trend was noted between the number of cigarettes smoked at age 43 and the rate of 10-year change in performance on a memory task. Based on such findings, the effects of smoking on cognitive function may seem at least partly direct rather than being totally mediated through either vascular or pulmonary pathology (a notion empirically demonstrated later by Whalley et al. (2005) in an investigation based on survivors of the Scottish Mental Health Survey). For example, it is possible that smoking may upset various cerebral blood flow parameters. On the other hand, the effects of smoking could be accounted for by other unknown mechanisms.

The value of giving up smoking for mental functioning in old age has been the focus of several epidemiological studies and an important line of research in this field. In the Caerphilly cohort (Elwood et al., 1999), no differences in cognitive performance were found between former smokers and never-smokers, and in the MORGEN study in the Netherlands (Kalmijn et al., 2002), scores on the Verbal Learning Test and the Stroop were found to be between those of current and never-smokers. Whereas Galanis et al. (1997) noted that the likelihood of scoring poorly on the CASI instrument was inversely related to the time since quitting smoking in elderly Japanese-American men, it has also been pointed out that giving up smoking may be related to a reduced rate of decline in specific cognitive functions (Richards et al., 2003).

Body Weight

Increased body weight is associated with elevated risk of premature cardiovascular mortality and morbidity, including stroke. In particular, obesity is a risk factor for hypertension and type II diabetes, and may be related to disturbed blood lipid levels. In this context, a relationship might also exist between body weight and cognitive function. For example, body weight may act as a moderator of vascular risk factors, including hypertension (Elias et al., 2001). However, it has also been suggested that overweight might contribute more directly to impairment in cognitive function, perhaps through its pro-inflammatory potential (Jeong et al., 2005), eventually leading to structural brain changes (Jagust et al., 2005). Despite the biological plausibility of such an association, a recent review of the epidemiological literature underscored the relative paucity of studies in this area (Elias et al., 2001).

In an early population-based study of older men, an absence of a linear association between the body mass index (BMI) and performance on a global cognitive task was noted (Kilander et al., 1997). However, a high BMI (>28.6) was moderately associated with lower performance, independently of age, education, occupation, and history of stroke. Similarly, a sex-specific analysis based on data from the Framingham Study demonstrated poorer mental ability in obese individuals (BMI $\geq$ 30) (Elias et al., 2005). After control for sociodemographic and vascular risk factors, obese men scored relatively worse on a global composite score, and on the WAIS visual reproductions and digit span backwards subtests. Relative to subjects with a BMI of less than 23, those with a BMI equal or greater than 25 had poorer mental status scores, but these results were limited to participants with a waist circumference of more than either 80 (women) or 90 cm (men) (Jeong et al., 2005). In subjects with low abdominal obesity, a BMI level between 23 and 25 was associated with lower global ability scores. In contrast to these findings, a study involving community-resident older men failed to establish an association between BMI and measures of global ability and information processing speed after controlling for multiple confounders (Alemann et al., 2005).

Physical Inactivity

Whether physical inactivity is associated with impairment in cognitive function in old age has been the focus of study in a number of investigations. In an early observational study by Rogers et al. (1990), a greater 4-year decline in bi-hemispheric cerebral blood flow was observed in physically inactive retired, elderly subjects after annual blood flow measurements. In contrast, subjects who maintained a high level of physical activity over the study interval experienced no decline in cerebral blood flow. Moreover, performance on a global cognitive task, the Cognitive Capacity Screening Examination, was significantly worse in the physically inactive group. In a study by Hultsch et al. (1993) cognitive function was examined in 484 men and women aged 55-86 years who self-reported participation in physical activities. Using linear regression analysis, a positive, statistically significant association was found between levels of physical activity and performance on measures of verbal fluency, word recall, and text recall. In other words, more exercise was associated with better cognitive performance. In addition, exercise levels were inversely associated with performance on tasks assessing semantic processing time and comprehension time.

In another investigation, in which 858 Australian community-resident elderly subjects were administered a cognitive test battery, moderate positive associations were observed between self-reported and informant-reported activity levels and performance on both global and domain-specific cognitive tests (Christensen et al., 1996). In particular, for certain timed tasks, a significant interaction between level of activity and age were found, suggesting that participation in physical activities may offset the effects of age on these cognitive measures. In doing so, it has been suggested that greater exercise may lower vascular risk and/or directly stimulate the growth of neurons and prolong their survival (Yaffe et al., 2001). It must be noted, however, that in all these studies, a single summary score capturing a large number of different leisure activities was used for the computation of exposure status. In some instances, other activities than those strictly physical in nature were included. As a result, important aspects of the assessment of the level of exercise, including its type, intensity, and duration, were unavailable to these analyses.

Perhaps in response to the limitations experienced by the studies above, a series of recent reports have investigated the above relationship in more detail, and what is likely to be of importance for health promotion strategies, the impact of commonly performed everyday activities on mental performance. For example, in the Study of Osteoporotic Fractures (SOF) (Yaffe et al., 2001), cognitive function was assessed with the MMSE at baseline and follow-up six to eight years later in 5925 community resident women. A major objective of the study was to examine the relationship between performance and decline on the MMSE and baseline physical activity levels (blocks walked and total kilocalories expended per week). The results demonstrated a significant trend whereby greater levels of exercise were associated with less risk of cognitive decline. Moreover, for every mile (approximately 1.6 kilometres) walked per day, women had a 13% lower risk of decline. Similar levels of reduced risk were associated with every standard deviation of total kilocalories expended per week.

Pignatti et al. (2002) also noted that high baseline levels of physical activity (walking at least two kilometres a day) were associated with decreased decline on the Mental Status Questionnaire over 12 years of follow up in elderly Italian women. Lastly, in a large sample of over 16000 women recruited to the Nurses' Health Study, in which physical activity was based on a series of measures prior to cognitive testing, a positive association between the two was observed (Weuve et al., 2004). Specifically, a significant relationship across quintiles of physical activity was noted for both measures of global cognitive ability and specific cognitive functions. The mean differences across quintiles of exposure were equivalent to the mean differences that were observed for women two to three years apart in age. With respect to walking, differences in cognitive scores associated with walking at an easy pace for at least one and a half hour a week (compared to less than 38 minutes a week) were equivalent to those that were observed for women approximately one and a half years apart in age. Multivariate adjustment did not materially affect the findings which also were observed when subjects with extreme values were excluded from the analyses. Whether the above observations are also applicable to men remains to be tested. In sum, however, these results do strongly point to the role of low-intensity everyday exercise levels in the preservation of intellectual processes of elderly people.

Diabetes

Diabetes mellitus is characterised by elevated circulating blood glucose levels (hyperglycaemia), which through damage to small and large blood vessel, may lead to premature vascular and neurological complications. The adverse influence of type I diabetes on cognitive function in adults has been well established (Ryan, 2001). In contrast, the relationship of type II diabetes with neuropsychological processes has only been investigated more recently. Whereas the focus of studies of type I diabetes has mostly been on the cognitive effects of intensive glycaemic control (hypoglycaemia and/or hyperinsulinaemia), type II diabetes studies have largely concentrated on the role of the disease itself (Asimakopoulou et al., 2002). With respect to the latter, contradictory findings regarding an association with cognition have widely been found (Kalmijn et al., 1995; Perlmuter et al., 1984; Robertson-Tchabo et al., 1986). A recent review which was based on over 20 studies highlighted a number of methodological shortcomings of published reports (Strachan et al., 1997). Despite this, in a majority of studies, type II diabetes was found to be negatively associated with at least one aspect of cognition in middle-aged and older individuals. Accordingly, the most consistent association reported was with tasks of verbal memory, but also with measures of global or other domain-specific abilities.

Cognitive deficits in relation to type II diabetes have further been shown in subsequent reports, some of which have addressed the methodological limitations of earlier investigations. For example, an analysis based on the Framingham Study found diabetic subjects more likely to perform poorly (below the 25^{th} percentile) on the delayed recall component of the WAIS logical memory test (Elias et al., 1997). Performance on the other WAIS subtests did not vary with disease status. Small but significant differences in verbal memory (immediate recall only) and mental flexibility were also reported in a methodologically rigorous comparison of subjects with and without type II diabetes, matched on age, sex, IQ, morbidity, and medication use (Asimakopoulou et al., 2002). Moreover, in a large-scale study of elderly women, the largest effects of diabetes were observed on immediate and delayed word recall (Crooks et al., 2003).

In contrast to the above, the finding of a selective deficit in memory associated with type II diabetes was not corroborated in a large sample of middle-aged male and female civil servants (Kumari and Marmot, 2005). It was noted, however, that the absence of an association with memory might be due to the relatively young age of the cohort. Possibly, the negative effects of diabetes on memory might not be sufficiently manifest at this age level. Alternatively, memory might predominantly be affected by medical comorbidity rather than diabetes per se, and if so, the relatively low prevalence of diabetes complications in middle-age may partly be responsible for these results. With respect to this latter point, there is some evidence suggesting that the effects of type II diabetes-associated vascular complications on cognitive performance in elderly people may actually be less detrimental than those related to poor glycaemic control (Gradman et al., 1993; Sommerfield et al., 2004; Gallacher et al., 2005).

2.5.4. Other Modifiable Risk Factors

Peak Prior Cognitive Ability

In addition to influence of adult social circumstances on cognitive function (reviewed in a later section), a growing body of evidence suggests socioeconomic conditions in early life may also be important for subsequent intellectual development and levels of functioning in adulthood (Luo and Waite, 2005; Singh-Manoux et al., 2005). In a series of recently published reports, markers of childhood socioeconomic circumstances have been positively associated with indicators of childhood health (Luo and Waite, 2005), adult educational attainment (Richards and Wadsworth, 2004), and socioeconomic status (Singh-Manoux et al., 2005), all of which may act as major determinants of physical and psychological functioning in old age. In other words, childhood socioeconomic conditions may greatly influence adult living and working conditions, and it could be through such circumstances that social inequalities in old-age levels of functioning and health are realised.

There is also, however, evidence of more direct effects of poor childhood conditions, such as low socioeconomic status (Kaplan et al., 2001; Luo and Waite, 2005) and adverse home conditions (Richards and Wadsworth, 2004) on both levels of performance and the rate of decline on global and domain-specific cognitive measures in middle-aged and older adults. Despite some contradictory evidence (Singh-Manoux et al., 2005), these findings are in support of the perspective that childhood socioeconomic status may have long lasting imprint on cognitive functions irrespective of other experiences over the intervening years. In these terms, a more advantageous socioeconomic environment in early life may directly affect cognitive development, possibly through a greater exposure to cognitive stimuli (Everson-Rose et al., 2003), thus providing a buffer against cognitive deterioration in later life. On the other hand, childhood socioeconomic status may act as a proxy for 'cognitive reserve' or pre-morbid cognitive ability (as discussed by Richards and Deary (2005), and already mentioned herein, the brain's "cognitive reserve" concept maintains there are aspects of brain structure and function that can buffer the effects of neuropathology such that the greater the reserve, the more severe the pathology must be to induce functional impairment).

Employing more proximal indicators of cognitive reserve, several studies have demonstrated a relation of levels of childhood ability, as estimated from performance on mental ability tests, with diverse health outcomes in later life. For example, lower ability levels are related to an increased risk of all-cause and cause-specific mortality and morbidity (Batty et al., 2005; Deary et al., 2004; Hart et al., 2003; Hart et al., 2004), greater frailty (Deary et al., 2004), and poorer quality of life (Bain et al., 2003). In contrast, higher ability is associated with less cognitive decline in adult life (Richards et al., 2004), even though an earlier study, using less precise methods, failed to confirm this (Rabbitt et al., 2003). In a study of men and women born in 1946, Richards et al. (2004) noted an inverse relationship between measured ability levels at age 15 and the rate of decline on tasks of memory and search speed from age 43 to 53 years. More importantly, these results were observed after later-life educational and occupational attainment as well as several health indicators were statistically controlled for.

In sum, these findings suggest that childhood cognitive ability, vastly shaped by early-life socioeconomic conditions, exerts important influence on adult intellectual capacity, possibly through its relation with adult socioeconomic attainment and associated exposures, but also independently, by providing greater resistance to the effects of diverse pathological insults.

Educational Level

A substantial body of literature now exists on the relationship between early-age educational attainment and cognitive function in later life. The finding of a strong positive association between years of formal education and better cognitive performance, and less decline, has almost been the norm across various population-based epidemiological studies (Lee et al., 2003; Seeman et al., 2005; Wight et al., 2002). Moreover, such an association has been noted in both representative (Cagney and Lauderdale, 2002) and selected (Lee et al., 2003; Seeman et al., 2005) study populations, in men (Wight et al., 2002) and women (Lee et al., 2003), and in different ethnic groups (Cagney and Lauderdale, 2002).

In several cross-sectional reports, higher scores on global measures of cognition were found to be positively related to level of education. In the MRC CFS Study (Anonymous, 1998), baseline MMSE scores increased as the number of years of full-time education completed increased. Time spent in full-time education was negatively associated with the proportion of subjects showing cognitive impairment. Similar cross-sectional findings were demonstrated in the MacArthur Studies of

Successful Aging (Seeman, 2005), the Nurses' Health Study (Lee et al., 2003), and in the National Longitudinal Surveys of Older Men (Wight et al., 2002). Findings from studies that have collected longitudinal data on specific cognitive abilities have lent further support to the above results, even though differences in study populations and cognitive tasks may be the underlying reason for the observed heterogeneity regarding what aspects of cognition may be involved. For example, formal educational attainment was highly positively associated with performance on all five measures of both crystallised and fluid abilities in elderly men and women in the MacArthur Studies of Successful Aging (Seeman et al., 2005), but only with measures of psychomotor speed in the Leiden 85-plus Study (and not with memory functions) (van Exel et al., 2001).

On the other hand, in the CC75C study (Cullum et al., 2000), an inverse association between the rate of 4-year decline and level of education was only observed for the CAMCOG Memory subscale. Despite such inconsistencies, the mere fact that an association is consistently found between education level and cognition has prompted an inquiry into the potential mechanisms for this relationship.

Several hypotheses have been proposed to account for the relationship between education and cognitive function (Lee et al., 2003; Seeman et al., 2005). For example, one explanation states that education may serve as a marker for other education-related factors, including health status and lifestyle choices (Seeman et al., 2005). In most studies, however, an education-cognition association has been found after the statistical control of numerous health and lifestyle-related indicators. In a second hypothesis, it is postulated that the relation of education with cognitive function is in fact artefactual, perhaps due to a cultural bias in the assessment of neuropsychological function or better test-taking ability of individuals with more formal education. Given that this association has been found in different ethnic cohorts, where access to formal education may vary substantially according to subjects' ethnicity, makes this an unlikely explanation (Cagney and Lauderdale, 2002). A third perspective, consistent with the 'use it or lose it' hypothesis, suggests that education may lead to occupations or personal and social environments which are more likely to include mental stimulation throughout the life-course. In fact, there is evidence for better cognitive ability in mid to late life in individuals who engage in leisure activities (Singh-Manoux et al., 2003) and continued education (Wight et al., 2002), even though the cognitive benefits of such activities may be most evident in those with the least formal education (Wight et al., 2002). Finally, it is possible that education may be associated with more direct influence on cognitive processes, perhaps through greater dendritic branching, ultimately resulting in more brain 'reserve' capacity. Despite the challenges involved in testing this last hypothesis, based on the current empirical evidence, the first two seem unlikely explanations for the widely observed association between level of formal educational attainment during the formative years and cognitive function in later life (Cagney and Lauderdale, 2002; Seeman et al., 2005).

Socioeconomic Status

Socioeconomic variability in adult health has been well established and recently has the association with levels of cognitive ability gained interest. A prominent feature of the growing body of literature in this area is the use of heterogeneous indicators of socioeconomic status across studies, among them being level of education (Cagney and Lauderdale, 2002; Turrell et al., 2002), type of occupation (Cullum et al., 2000; Jorm et al., 1998), household income (Cagney and Lauderdale, 2002; Richards, 2004), and personal wealth (Cagney and Lauderdale, 2002). In this discussion, the focus is exclusively on non-educational indicators of socioeconomic status. Cross-sectional studies, investigating cognitive performance in relation to occupational social class, have found class level to be inversely associated with scores on measures of global ability, such as the MMSE (Anonymous, 1998; Gallacher et al., 1999). For example, lower occupational class was associated with a greater 4-year decline on the CAMCOG Attention/ Calculation subscale in the CC75C study of elderly people (Cullum et al., 2000).

A similar association to the above was noted with respect to the rate of 10-year decline on tasks assessing memory and search speed (in men only) in middle-aged adults (Richards et al., 2004). In this latter study, the association with social class was relatively weak. It is therefore possible, that the lifetime impact of occupation, and associated exposures, on cognitive processes in these middle-aged individuals may not have been fully realised at the time they underwent neuropsychological assessment. In a related enquiry carried out by Jorm et al. (1998), the cognitive effects of lifetime occupational activity rather than job-associated hazardous exposures, health behaviours, or access to medical care, were studied in a sample of men aged 70 years and more. Using a classification of occupations based on their psychological demand, an age and education-adjusted cross-sectional analysis demonstrated that the poorest relative performance on the MMSE, the Episodic Memory Test, and the Symbol-Letter Modalities Test, was in men who had worked for most of their lives in skilled trade, technical, and service occupations.

The use of occupation as an indicator of socioeconomic status has important limitations, particularly in studies involving people of retirement age (Cagney and Lauderdale, 2002). For example, commonly used scales based on salaried lifetime occupation may not rank women's occupations as appropriately as they do men's. Moreover, the most recent, or current, occupation of older people may itself reflect poor health and diminished levels of functioning. In response, more direct measures of socioeconomic status have been advocated. For example, positive associations were found between current household income and performance on a cognitive test battery in a cross-sectional analysis of the AHEAD survey of older people (Cagney and Lauderdale, 2002). Similar findings were reported for older Finnish men in the Kuopio Ischaemic Heart Disease Risk Factor Study (Turrell et al., 2002).

The above finding was not, however, corroborated in a more homogeneous sample of elderly women in the Nurses' Health Study (Lee et al., 2003). The lack of association in the last study may reflect the inherent limitations involved in using current household income as a measure of socioeconomic status of old people since it does not reveal significant income disparities that may have prevailed before retirement. This may be of particular relevance to elderly women whose socioeconomic status is closely tied in with their husband's occupation (Cagney and Lauderdale, 2002). Moreover, current household income does not reflect the value of accumulated assets, such as property and personal savings, which may act as a better indicator of cumulative socioeconomic influence over a person's lifespan (Cagney and Lauderdale, 2002). Turrell and colleagues (2002), who advocated a life-course perspective in the study of cognitive ability in adulthood, reported on the consistent impact of socioeconomic mobility over the life-course on late-life mental functioning: better cognitive performance was observed for men who occupied a disadvantaged childhood status and then demonstrated upward mobility over the life-course than those of similar status in childhood but did not show such upward change. Similarly, subjects of high childhood socioeconomic status but who later experienced downward mobility were cognitively worse off in later life than those who maintained a similar position throughout life. Also, the number of times subject's found themselves in a low socioeconomic position over the life-course was strongly and inversely related to performance on both global and domain-specific cognitive tasks.

Although the exact mechanisms of such an association has yet to be identified, these findings are in support of a general hypothesis which proposes that cognitive ability in late adulthood may be shaped through the positive or negative influence of exposures over time, including those that are associated with socioeconomic status at different stages during the person's lifespan (Richards and Deary, 2005; Turrell et al., 2002).

Alcohol Consumption

In early investigations of the relationship of alcohol with mental outcomes, heavy drinking was found to be associated with an increased risk of cognitive impairment (Saunders et al., 1991). In more recent studies, the interest has been on the long-term effects of regular, moderate alcohol intake on cognitive processes. So far, however, findings have been mixed. For example, in the Zutphen Elderly Study (Launer et al., 1996), moderate drinking (<26.4 grams of alcohol) per day in the preceding month) was associated with a lower risk of poor performance on a global ability test. In contrast, no relationship was found between the amount of alcohol consumed and performance on several cognitive tests, including the MMSE, in the Caerphilly cohort study (Elwood et al., 1999). One possible explanation for this discrepancy may be that, in the former analysis, the comparison group included both lifetime abstainers as well as ex-drinkers. Indeed, the lowest intake category was preferred as the reference level in the Caerphilly study since former drinkers were found to have both worse cognitive function and more co-morbidity. However, in a third study, essentially no change in results was observed when abstainers were excluded and the analysis repeated using the lowest drinking category as reference (Kalmijn et al., 2002). In this cohort of elderly Dutch men and women, a U-shaped association was noted between the level of alcohol consumed and cognitive performance. Subjects who had either 1-2 or 2-4 drinks a day scored relatively better on timed tasks assessing psychomotor speed and flexibility. Interestingly, a linear relationship was only observed in women, none of whom was in the heaviest drinking category (more than eight drinks a day).

Given that the pattern of alcohol use is likely to differ for men and women, sex-specific analyses of the association with cognitive function have been encouraged (Elias et al., 1999). Based on such recommendations, the MORGEN study demonstrated better cognitive function in relation to moderate alcohol consumption in women but not in men (Kalmijn et al., 2002). Moreover, in a French study based on 1389 elderly men and women (Dufouil et al., 1997), low to moderate alcohol levels (less than five drinks a day) were cross-sectionally associated with better overall cognitive performance in women; a positive, linear association was also reported with scores on six out of the 10 tests used, including the MMSE and the Digit Symbol Test. In contrast, no association was found in men.

Several hypotheses have been proposed in order to account for the sex differences in the relation of alcohol with cognitive function, most of which focus on sex differences in alcohol metabolism and alcohol-related risk behaviours. However, a more recent study found both male and female current drinkers to perform better on a task of global cognitive ability relative to abstainers and former drinkers (Bond et al., 2004). In addition, current drinking at baseline was associated with less 4-year decline in global cognitive performance. It is likely that the discrepancy between these and the findings reported above can be attributed in part to differences across studies with respect to the population examined, methods of assessing exposure to alcohol, neuropsychological tests, and handling of potential confounding factors. Before embarking on a search for causal mechanisms, future research needs to adequately address these methodological challenges associated with the problem under study.

Anxiety

The understanding of the importance of mood for normal cognition has greatly increased through decades of research. Specifically, it has been postulated that anxiety, which is characterised by feelings of apprehension, fear or nervousness, may interfere with cognitive processes by producing worry and other intrusive thoughts that compete for resources associated with the efficiency of processing, rather than storing, information (Eysenck and Calvo, 1992).

The empirical data of an association between anxiety and neuropsychological function in adulthood largely comes from cross-sectional studies, and only recently has anxiety been investigated as a predictor of cognitive decline for the first time. In a large, prospective study of elderly Swedish subjects, Wetherell et al. (2002) demonstrated an inverse association between baseline anxiety levels (based on performance on the State Anxiety subscale of the State-Trait Personality Inventory, STPI) and performance on tests assessing visual learning (Names and Faces, and Thurstone's Picture Memory), forced-choice vocabulary (Synonyms), verbal reasoning (Analogies), and visuospatial ability (Block Design). Tasks based on pattern matching (e.g. Digit Symbol), visual reasoning (Figure Logic), or general knowledge were not affected by greater anxiety. In contrast, the study failed to link neuroticism (based on the Eysenck Personality Inventory Neuroticism scale), which was used as a proxy for anxiety trait or proneness rather than current anxiety, with the rate of decline in cognitive test performance over a six-year interval when control for multiple covariates was made. Even though the study was limited in its approach to assessing anxiety and neuroticism, its findings suggests that anxiety may not be a long-term predictor of cognitive decline in elderly people. Rather, the presence of anxiety may simply affect test performance on specific cognitive tasks which require complex attention and coordination skills.

Results from a subsequent clinic-based study, which followed a group of cognitively-intact elderly people for a mean of 3.2 years, are somewhat in conflict with the assumptions raised above (Sinoff and Werner, 2003). Using a path analysis, the interaction between complaint of loss of memory, anxiety, depression, and cognitive decline on the MMSE, was examined. Excluding cognitively impaired participants (MMSE score <24), the study demonstrated independent effects of baseline anxiety levels on the rate of decline in global cognitive performance. In addition, anxiety was also found to affect cognitive decline indirectly, through greater levels of depression. Interestingly, the effects of subjective memory loss, as assessed by self-report at baseline, on cognitive function were entirely mediated by anxiety in these models. Despite the inherent difficulty in determining the direction of the anxiety-cognition association, the case has been made that anxiety may occur as a result of early cognitive changes, and therefore act as an early predictor of future cognitive decline. However, more prospective evidence is greatly needed where, for instance, both the characteristics and duration of anxiety are carefully assessed at different points in time.

Depression

Depression, which may be defined as the inability to experience pleasure, is likely to be both under-diagnosed and insufficiently managed in older people (American Psychiatric Association, 1994; Paterniti et al., 2002; Stewart, 2005). There is, however, increasing evidence suggesting it may be an important and treatable risk factor for cognitive dysfunction in the elderly. It has been pointed out that depression may comprise subtypes that differ by diagnostic criteria as well as by their response to treatment, even though few studies have systematically examined these in relation to neuropsychological function (Airaksinen et al., 2004; Willner, 1984). Different depression subcategories are, however, all likely to share the main symptoms of depressed mood, including difficulty in initiating responses and in sustaining effort or concentration, which may be of particular relevance to performance on cognitive tasks involving psychomotor speed, learning, and memory.

It is also possible that impaired cognitive function in depressed individuals may be directly related to the disease itself and its neuropathological aspects. This hypothesis received support in a small-scale study where in the first instance, the neuropsychological test performance of cognitively-intact (CAMCOG score of 92 or more) patients with clinical depression was compared to that of healthy controls (Brown et al., 1994). In comparison to controls, depressed patients performed more poorly on a number of tasks assessing language, memory recall and recognition, attention, and behavioural regulation. In a subsequent step, which was based on comparing borderline (CAMCOG score between 82 and 91) and cognitively-impaired (CAMCOG less than 81) depressed patients to a group of unimpaired depressed subjects, both patient groups showed significant deficits on tests involving immediate recall and attention. In this analysis, the poorest relative performance was seen in depressed subjects who were classified as being cognitively impaired. Disease severity, symptomatology, or treatment, did not have an effect on cognitive performance in depressed subjects.

Although a negative cross-sectional association between depression and cognitive function has consistently been observed in large population-based studies (Fuhrer et al., 1992), it remains to be determined whether depression has a role in predicting later-life intellectual decline. In an early study based on community-resident elderly men and women, self-reported depressive symptoms at baseline did not predict risk of decline in SPMSQ performance over a period of 12 years (Bassuk et al., 1998), although an association was noted in subjects who experienced mental decrements post-baseline. Similarly, Major Depressive disorder was not associated with the rate of decline in MMSE performance over an 11-year period in young to middle-aged participants in the Epidemiologic Catchment Area Study (Rosenblatt et al., 2003).

Whereas the findings reported above seem to go against the notion that depression may precede cognitive decline in time, evidence from other investigations have been more supportive. For example, Yaffe and associates (1999) found a significant dose-related association between the number of self-reported depressive symptoms and the rate of 4-year decline in performance on three cognitive tasks (the modified MMSE, the WAIS Digit Symbol, and the Trails B) in non-demented elderly women. Importantly, the association remained when baseline cognitive ability, health, and functional status, were controlled for in multivariate models. Self-reported depressive symptoms were also related to cognitive decline in both the EVA study cohort (Paterniti et al., 2002) and in a prospective study involving a bi-racial population (Wilson et al., 2005). In the earlier study, an association with 4-year decline in global cognitive performance was only found in those subjects who reported persistent (depressed at baseline and follow-up), rather than episodic (depressed only at baseline), depressive symptoms. These analyses were based on subjects who were considered cognitively-intact based on their baseline MMSE performance (score of 26 or greater).

Although it is likely that methodological differences may be the cause of the inconsistency found between published studies, and particularly with respect to the assessment of depressive symptoms (Stewart, 2005; Wilson et al., 2005), little is still known about the basis of this relationship. As a result, three possible explanations have been proposed (Comijs et al., 2001). Whilst the first suggests depression may be a psychological reaction to early subclinical cognitive decline, the second emphasises a shared nervous system pathology underlying depression and cognitive dysfunction, possibly one which has a predilection for either subcortical and/or prefrontal cortical structures (Butters et al., 2000). Lastly, it has been pointed out that depression may be associated with elevated levels of cortisol which may lead to dysregulation of the hypothalamic-pituitary-adrenal axis (HPA). Judging from the available empirical evidence, however, the first of these is unlikely to be the sole explanation.

2.5.5. Novel Risk Factors

Homocysteine

The past decade has seen a growth in the number of studies of the relationship between plasma concentrations of homocysteine and performance on cognitive tasks in adulthood. Homocysteine is an amino acid that is generated in the metabolism of methionine, a sulfur-containing amino acid, a process dependent on particular vitamin B fractions (folic acid and cobalamin). In this respect, plasma homocysteine levels are considered to be a good marker of the functional status of cobalamin and folic acid in body tissues (Nilsson et al., 2001). An elevation in homocysteine levels is frequently observed in patients with deficiency in one or more of these vitamins. Accumulation of homocysteine in the plasma may exert direct neurotoxic effects and/or induce atherogenesis in vascular structures (Garcia and Zanibbi, 2004).

Early population-based studies relating homocysteine levels with cognitive function were small and based on cross-sectional analyses. Mixed results were frequently reported. For example, no association with performance on global (the MMSE) and domain-specific tasks was found in an Italian study involving 54 subjects aged 65 years and older (Ravaglia et al., 2000). On the other hand, a small-scale study based on 156 community-dwelling UK elderly showed an inverse, linear association between homocysteine levels and CAMCOG test scores (Budge et al., 2000). These analyses, which controlled for age, sex, pre-morbid ability, and depressed mood, suggested a 3-point decrease in CAMCOG scores for every 10 μmol/L increase in plasma homocysteine levels. In contrast, no relationship with MMSE scores was observed. Similar findings of an inverse cross-sectional relationship between homocysteine levels and performance on global (Ravaglia et al., 2003; Wright et al. 2004) and domain-specific (Schafer et al., 2005) tasks have been reported in subsequent publications. In the last of these, the Baltimore Memory Study, the homocysteine effects on cognitive performance were large: on average, an increase in homocysteine from 7.6 μmol/L (25^{th} percentile) to 11.3 μmol/L (75 percentile) was equivalent to an increase of 4.2 years in baseline age (Schafer et al., 2005).

In order to verify the direction of the relationship of homocysteine with cognitive function, large-scale, prospective epidemiological studies need to be carried out. To date, however, few exist. Moreover, it is not clear whether it is through neurotoxicity, vascular effects, or folic acid and/or cobalamin insufficiency that elevated homocysteine levels are negatively related to intellectual performance. However, based on data from 70 male participants in the Normative Aging Study, an inverse association between plasma homocysteine levels and spatial copying skills was observed (Riggs et al., 1996). Whereas the results were not accounted for by clinical diagnosis of CVD, the association no longer remained once blood levels of both folic acid and cobalamin were statistically controlled for. Similar findings were observed in the MacArthur Studies of Successful Aging cohort (Kado et al., 2005). In both cross-sectional and a 7-year longitudinal analyses of cognitive ability, no association with baseline homocysteine levels was found when vitamin B status was taken into account. In other words, the effects of homocysteine levels on cognition were largely explained by low folic acid levels. Identical findings had been replicated by some researchers (Almeida et al., 2004) but not others (McCaddon et al., 2001; Miller et al., 2003; Wright et al., 2004). This inconsistency in findings across studies is likely to be in part due to differences in study populations, methods of assessment of homocysteine and vitamin B levels, the overall lack of serial blood level measures, handling of potential confounders, and differences in neuropsychological tasks.

Inflammatory Markers

A limited but growing body of published work currently exists on the relation of plasma and serum markers of inflammation and haemostasis with neuropsychological function in the elderly. Inflammation is central to atherosclerosis and elevated blood levels of inflammatory markers have been associated with an increased risk of acute coronary disease and stroke (see section Risk Factors for Atherosclerosis). In addition, it has been suggested that pro-inflammatory proteins in the periphery may directly promote neuroinflammation, ultimately leading to cognitive impairment.

Further evidence in support of a relationship between inflammatory activity and cognitive function has come from epidemiological studies. For example, in a cross-sectional analysis of data from the Conselice Study of Brain Aging, a community-based study of Italian elderly, subjects with MMSE scores of 24-25 and 26-28 had significantly increased odds (relative to subjects with an MMSE score of 29-30) of baseline serum CRP levels greater than 0.7 mg/dL (highest decile of CRP) (Ravaglia et al., 2005). Despite the low numbers of low-scoring subjects with high levels of CRP, these analyses controlled for age, sex, education, fibrinogen, leukocyte count, albumin, BMI, edentulism, and co-morbidity. These findings are further supported by data from the Longitudinal Aging Study Amsterdam (LASA) (Dik et al., 2005). A cross-sectional analysis adjusting for age, sex, and education revealed less verbal items recalled in subjects falling into the middle (141-172 % normal human plasma, NHP) and highest tertile (173-437 % NHP) of baseline levels of the inflammatory marker α_1-antichymotrypsin. However, no relation with other cognitive measures was noted, including the MMSE. High levels of the pro-inflammatory cytokine IL-6 (IL-6) (5.0-76.0 pg/mL) and CRP (5.3-171.0 μg/mL) were not associated with performance on any of the cognitive tasks used.

On the basis of longitudinally-collected data on cognitive function, inflammatory processes have further been associated with an increased decline in cognitive test performance. In the MacArthur Study of Successful Aging, both the largest 2.5-year and 7-year shift towards lower values in median cognitive test scores (a single score was used which was based on several cognitive tests that were combined in order to indicate the highest cognitive function possible in the individual) occurred in subjects with the highest baseline values of IL-6 (highest tertile) (Weaver et al., 2002). Further analyses showed that in the final fully-adjusted model, the 2.5-year risk of decline (defined as having a change score in the bottom tertile of the overall change distribution for the full sample) was significantly elevated in subjects in the highest (OR=2.03; 95% CI=1.30-3.19) and the middle (OR=2.21; 95% CI=1.44-3.42) tertiles. A significantly higher 7-year risk was only observed in the highest IL-6 tertile (OR=1.90; 95% CI=1.14-3.18).

Similarly to the above, a linear regression analysis (controlling for age, sex, and education) based on data from 92 subjects in the Maastricht Aging Study demonstrated how baseline levels of the serum inflammatory markers haptoglobin and CRP predicted steeper six-year decline in performance on mental tests assessing attention and executive function (Stroop test), immediate (CRP only), and delayed recall of verbal material, in persons 50 years and older (Teunissen et al., 2003). Additional work has provided evidence of an inverse relation of baseline levels of IL-6 and CRP (Yaffe et al., 2003), D-dimer (Wilson et al., 2003), and α_1-antichymotrypsin (Dik et al., 2005), with the rate of decline in performance on global cognitive tasks.

Rheological Factors

Diverse changes in vascular and haemorheological properties accompany ageing which may affect the flow of blood in vessels. In addition to alterations of the blood vessel walls themselves, as indicated by greater arterial stiffening, decreased vascular tone, and decreased vessel diameter, changes in rheological parameters include increases in blood viscosity, the intrinsic resistance of blood to flow, and its major determinants (haematocrit, plasma viscosity, and red cell deformability/aggregation) (Ajmani et al., 2000). Additional negative influence on blood viscosity could come from exposures to cigarette smoking, high blood pressure, and elevated levels of circulating plasma lipids/lipoproteins. Possibly through the rheological effects of high blood viscosity on atherothrombogenesis or ischaemia distal to atherothrombotic stenosis (Lowe, 2003/2004), elevated levels of haematocrit, plasma viscosity, and erythrocyte sedimentation, have been positively associated with the degree of carotid artery atherosclerosis (Lee et al., 1998), the risk of coronary events (Lowe et al., 1997; Yarnell et al., 2004), and stroke (Lowe et al., 1997). In addition, erythrocyte deformability is a major determinant of blood flow in the microcirculation and, if reduced as is in sickle-cell disease, has been implicated in the aetiology of MRI-determined cerebral infarctions/ischaemia (Moser et al, 1996; Simchon et al, 1987).

With respect to the aforementioned, a link between blood rheology and cognitive function may seem plausible. For example, relative to age-matched controls, more errors associated with maze learning have been noted in rats treated with erythropoietin, resulting in large increases in haematocrit levels (Ajmani et al., 2000). The effects may be age-dependent, suggesting more susceptibility to haemorheological stress in older age. Unfortunately, few published accounts exist on the relationship between rheological factors and cognitive function in elderly people. In fact, only in the Caerphilly study has this association been investigated in a population context (Elwood et al., 2001). A cross-sectional analysis was carried out on the association between haematocrit, fibrinogen, plasma viscosity, and performance on tests assessing verbal and mathematical reasoning (AH4) and choice reaction time. The study demonstrated that, whereas no association was observed between haematocrit and AH4 test performance, a U-shaped relationship existed with reaction time. Specifically, reaction time improved with increasing haematocrit levels (up to 46%) and then decreased with any further increase. In addition, statistically significant linear trends, adjusted for age and social class, were also observed for both tests across quartiles of plasma viscosity. A difference of approximately 23% (AH4) and 12% (choice reaction time) of a standard deviation was found between men in the highest and lowest quartile of plasma viscosity, respectively. In contrast, fibrinogen levels were not related to performance on either task.

2.5.6. Section Summary

A large and growing part of the research in the area of cardiovascular disease and cognitive function has been dedicated to investigating the role of atherosclerotic risk factors in intellectual dysfunction. Over recent decades, and despite conflicting results at times, a number of studies have convincingly demonstrated the contribution of such factors to reduced levels of cognitive function in middle-aged and elderly people. There is also evidence that several potentially modifiable vascular risk factors may be associated with an increased decline in cognitive ability over time, which may have implications for strategies aimed at delaying or preventing cognitive deterioration in the population. Another outcome of this research effort has been the increase in studies suggesting that physical activity and smoking cessation, among other things, may have beneficial effects on adult cognitive function. However, further interventional studies which build on existing observational data are greatly needed.

Despite being studied separately, many atherosclerotic risk factors, as well as those exerting a positive influence on cognitive function, are likely to co-exist within the same individual. Few studies have examined the combined effects of several risk factors on cognitive processes. Whereas each of the major risk factors, including blood pressure, smoking, blood lipids, and diabetes, may independently be associated with intellectual impairment, the cognitive effects of these are also likely to be mediated in part through their influence on atherosclerotic vascular pathology. As a consequence, targeting such factors through appropriate interventions may possibly be the single most important step towards halting or delaying cognitive decline. On the other hand, in investigations of cognitive functions in patients with vascular disease, most if not all of the factors reviewed in this chapter are likely to operate as potential confounders of the association under study.

CHAPTER THREE

Aims and Objectives of Study

3.1. STUDY BACKGROUND

Human cognitive ageing is characterized by large inter-individual differences in the rate of intellectual change. Although many individuals maintain their prior levels of cognitive ability well into the last decades of life, some may even experience an improvement in specific skills. On the other hand, deterioration in cognitive processes frequently accompanies ageing. Intact mental function in old age is fundamental to normal physical self-maintenance, successful social interactions, and performance of everyday tasks (Bell-McGinty et al., 2002). As a result, even mild intellectual deficits may induce functional impairment (Plehn et al., 2004). Progressive decline in cognitive function may also lead to dementia which is a major cause of increased dependency and institutionalisation of elderly people (Melzer et al., 1997; Neale et al., 2001). Treatment options for cognitive impairment are limited at present and finding ways to prevent or delay its onset in old age is regarded as a public health priority (Purandare et al., 2005; Román, 2003). Linking potentially amenable predictors to early markers of cognitive impairment is likely to be an important part of such a strategy. Specifically, performance on cognitive measures may be predictive of intellectual impairment by up to a decade later (Cervilla et al., 2004; Grober et al., 2000). Acting as possible markers of sub-clinical impairment, neuropsychological tests have a key role to play in assessing the effects of diverse exposures on brain functioning in elderly people.

The pattern of individual differences in mental ability in old age underscores the importance of person-specific factors in its aetiology. In recent years, there has been a growing interest in the investigation of the contribution of atherosclerotic vascular disease to patterns of adult cognitive function. A finely tuned relationship exists between the brain and the circulatory system, which if upset by vascular pathology, may disrupt normal neurocognitive processes (Tarter, Edwards, Van Thiel, 1988). Further to the biological plausibility of an association with cognitive function, the interest taken in vascular diseases is also likely to reflect their general importance in adult morbidity and mortality, their high prevalence in the older population, the possibility of their modification and prevention, and the clarity with which they may be conceptualised, detected, and diagnosed, in the research setting.

Based on the present review of published investigations, it is apparent that several important gaps exist in our current understanding of the relationships between CVDs, vascular risk factors and adult cognitive function. Specifically, there is a need to quantify the effects of clinical vascular disease on cognitive decline in population-based samples of older people where cognitive performance of those with disease is compared with that of non-vascular controls. Also, from both an epidemiological and clinical point of view, it is of inherent interest to examine whether the pattern of intellectual ability varies with type of manifestation of atherosclerotic vascular disease and whether vascular disease predicts decline over time in different mental functions. With respect to the latter, few studies examining vascular-related decline in mental function have acknowledged current theoretical notions of the hierarchical structure of human cognitive abilities. A further major issue in the study of cognitive decline in individuals with clinical CVDs is whether any observed associations are either wholly or partly the result of influences exerted by concomitant vascular risk factors on cognitive processes. Similar challenges are likely to apply to findings from investigations of the relationships between vascular risk factors and cognitive outcomes in older people.

3.2. RESEARCH AIM AND QUESTIONS

The principal objective of the present study is to examine the relationship between clinical CVD, vascular risk factors, and cognitive function in older people. In particular, the EAS provides a suitable ground for addressing some of the fundamental shortcomings of previous investigations since its features:

1) A random sample from the elderly general population. The data are therefore based on survivors with CVDs who in addition are likely to differ substantially in both mental ability as well as risk factor profile.

2) Data on longitudinal change across different intellectual functions over a period of four years as well as on a validated estimate of peak prior cognitive ability allowing the further exploration of the putative decline in cognitive function from 'best-ever' level.
3) Data collected from various sources on the prevalence and incidence of different indexes of atherosclerotic CVD using validated objective methods and standard diagnostic criteria.
4) Data on a number of potential confounding factors of the associations under study.

The specific research questions underpinning the present study are listed below:

1) As a group, do older people with any major symptomatic (non-stroke) cardiovascular disease experience more cognitive decline than those without clinical vascular disease?

2) Do older people with major symptomatic cardiovascular disease in specific arterial sites (e.g. CHD, PAD, and stroke) show on average an increased cognitive decline relative to those without any major vascular disease?

3) Is clinical vascular disease associated with individual differences in decline in cognitive function when individual variation in demographic characteristics and prior cognitive ability is taken into account?

4) Is symptomatic cardiovascular disease further related to individual differences in cognitive decline independently of established and novel vascular risk factors?

5) Do vascular risk factors contribute to individual differences in cognitive decline independently of concomitant clinical cardiovascular disease?

6) What aspects of cognitive function (i.e. general ability versus specific functions) are primarily affected by cardiovascular disease and vascular risk factors?

CHAPTER FOUR

Study Methodology

4.1. INTRODUCTION

This chapter describes the baseline methodology and follow-up procedures employed by the EAS, which is the first population-based cardiovascular epidemiological study in the United Kingdom to principally focus on peripheral arterial disease in the lower extremities. Specifically, the chapter provides detailed information on the EAS study population, the procedures of recruitment at baseline, the layout of the baseline and follow-up clinical examinations, as well as on the measures taken in order to continuously monitor the occurrence of new cardiovascular events. In addition, the cognitive function testing that was carried out in 1998/9 and 2002/3 is discussed in depth, with a special emphasis on subject recruitment procedures, the measures taken in order to ensure consistency in the administration and scoring of cognitive function tests, and the description of the cognitive function test battery. Finally, the chapter draws to a close with a section discussing the ways data were stored, manipulated, transformed, and statistically described for the purposes of the present study. Moreover, the section provides an insight into the approach of the multivariate data analysis and the adoption of specific statistical techniques.

4.2. THE EDINBURGH ARTERY STUDY: BASELINE SURVEY

4.2.1. Study Design

The original aim of the EAS was to describe the distribution and determinants of symptomatic and asymptomatic PAD in the general population. A further objective was to investigate the relationship between PAD and ischaemic cardiac disease in the study sample. As a result, the first part of the study was a cross-sectional survey, subsequently followed by two follow-up clinical examinations (see appendix B for a diagram of study design). The study participants, recruitment procedures, and measurements at each stage of the study are described throughout subsequent sections.

4.2.2. Study Population

The study population of the EAS comprised 55-74 years old residents of the City of Edinburgh. A random sample of participants was selected from age-sex registers of 11 Edinburgh general practices representing the whole spectrum of socioeconomic strata in all parts of the city. Based on sample size calculations (see below) approximately 272 subjects were randomly selected from each general practice in age-sex specific, five-year age bands in order to generate equal numbers in each age group (34 males and females from each age band). Lists with 2720 patient names were obtained from the general practices which were scrutinised by general practitioners (GPs) for exclusion of subjects considered unsuitable for participation (for example, because of advanced mental or physical illness), who had changed general practice, or had died. Excluded subjects were replaced by other randomly selected participants (n=353; 13.0%).

4.2.3. Subject Recruitment

All eligible subjects were approached about attending an Edinburgh University clinic for medical examination (n=2709). Following publicity in the media, participants were sent a letter of invitation signed by the director of the study and by a partner in the relevant general practice. Subjects unable to attend the clinic were offered either free of charge transportation to the clinic or to be visited at home. Any travel expenses incurred by the participants were fully reimbursed. On receipt of an affirmative reply, subjects were mailed an appointment date, a map of the University area, and detailed description of the clinical examination. Those whose letters of invitation were returned by the post office were subsequently replaced by other randomly selected subjects (n=163; 6.0%). Non-repliers to the first invitation were sent a second invitation letter, and those who had confirmed participation but were unable to attend the examination were offered a new appointment at a subsequent date.

4.2.4. Sample Size Determination

Sample size calculations undertaken in preparation for the EAS revealed that approximately 1500 subjects would be required for the baseline cross-sectional survey carried out in 1987/8. This decision was made on the basis of the number needed to conduct a subsequent follow-up study (prospective cohort study) with a sufficient statistical power to detect differences in the incidence of vascular events in relation to baseline characteristics.

4.2.5. Ethical Approval

An ethical approval for the conduct of the EAS baseline clinical examination, and the subsequent follow-up study, was granted by the Lothian Health Board Ethics of Medical Research Sub-Committee for Medicine and Clinical Oncology. In addition, an informed signed consent was requested from each participant before undergoing clinical examination.

4.2.6. Baseline Examination

All eligible subjects were invited to a baseline examination which involved a detailed collection of sociodemographic information, medical history, and clinical data. The specific information sought and the methods used are described in the following sections.

Clinical Sessions

Clinical examinations were conducted during mornings, each weekday from August 1987 to September 1988 at an Edinburgh University clinic. Occasional out-of-hours clinic sessions were also held as required. Approximately ten participants were invited to each clinic session. All subjects were asked to fast from 11 pm the previous evening (only if they were not diabetic) and refrain from smoking for at least two hours prior to the examination. Each participant had two sets of clinical procedures undertaken by one of two teams, each comprising a nurse and a trained technician. Before the clinical examination, a self-administered questionnaire was filled in by each participant and read over for completeness by a member of the clinic team.

Baseline Questionnaire

The self-administered questionnaire consisted of multiple questions enquiring about personal characteristics (age, sex, and marital status), level of education (highest completed), occupational social class, smoking history, medical history, history of angina pectoris and intermittent claudication, exercise, diet, and alcohol consumption.

Coding of social class was made according to the Registrar General's classification, with female married subjects classified by their husband's occupation (OPCS, 1980). Retired and currently unemployed participants were coded according to their longest held employment. Furthermore, a Carstairs deprivation score was assigned to each subject, based on the postcode district classification from the 1981 census (Carstairs and Morris, 1989).

Smoking habits were based on self-report and items regarding information on both current and lifetime smoking status were included. Alcohol intake was also assessed by self-report, and participants were asked to record their intake over the past week by indicating the number of drinks they had consumed in each of three categories: beer, wine, and spirits. One unit of alcohol was defined as a half a pint of beer, one glass of wine or a single measure of spirits. This allowed the assessment of a typical week's alcohol consumption (units of alcohol consumed per week). The above measures were judged to be sufficiently accurate since the self-reported levels of both smoking and alcohol intake correlated with the mean thiocyanate concentrations and gammaglutamyl transferase activities in the blood (Fowkes et al., 1992).

Information on the presence of angina, MI and stroke was obtained by requiring subjects to recall a doctor's diagnosis of the condition. Assessment of current medical treatment was also made through direct questioning. The WHO's angina and intermittent claudication questionnaire was used to enquire about the presence and characteristics of pain in the chest and legs (Rose, 1962). Subjects were also asked about ever having had a doctor's diagnosis of diabetes and the use of injections or tablets for its treatment.

Clinical Measurements

Of the inflammatory and haemostatic markers examined, serum CRP was assessed immunologically with a high-sensitivity assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). Similarly, plasma levels of IL-6, intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), E-selectin, and D-dimer, were measured with high-sensitivity ELISA kits (R&D Systems, Oxford, UK; and for D-dimer AGEN (Parsippany, NJ, USA). Lastly, fibrinogen was assessed by a thrombin-clotting turbidometric method in a centrifugal analyzer. Intra –and inter-assay variability coefficients were CRP, 4.7% and 8.3%; IL-6, 7.4% and 8.8%; ICAM-1, 4.8% and 7.4%; VCAM-1, 4.3% and 8.5%; E-selectin 4.8% and 5.7%; D-dimer 10.0% and 12.0%; and fibrinogen, 5.0% and 7.0%. The measures undertaken in order to ensure quality of the analyses included repeating values outside the 95% normal range and using internal quality control plasma with each marker assay.

Whole-blood and plasma viscosities were measured in EDTA-anticoagulated blood at high shear rates (over 300/s) in a Coulter-Harkness viscometer at 37 °C. Haematocrit was measured using a Hawksley microcentifuge and reader. Serum total and HDL cholesterol and triglycerides were performed on a Roche Cobas

Bioanalyser. LDL cholesterol was calculated using the formula: LDL cholesterol=total cholesterol-HDL cholesterol-triglycerides/5.

Following blood sampling, subjects' standing height was measured once to the nearest 5 mm with a free-standing metal ruler on a heavy base, and weight, without shoes and outer clothing, was measured to the nearest 100g on a Soehnle digital scale. A 12-lead electrocardiograph (ECG) and rhythm strip were then taken using a Hewlett Packard 'pagewriter' electrocardiograph. The ECGs were independently coded at a later date by two trained staff using the Minnesota code (Prineas et al., 1982). A third member of staff checked the two results. In the event of disparity, the ECGs were coded for the third time. If the third code agreed with neither of the other two coders, the ECG was checked by a consultant cardiologist and a final code assigned following a discussion between the coders.

In the second set of procedures, participants were asked to rest for ten minutes in the supine position before their systolic and diastolic blood pressure was taken in the right arm using a Hawksley random zero sphygmomanometer. The femoral, posterior tibial, and dorsalis pedis arteries were palpated in both legs for peripheral pulses. Ankle systolic blood pressure was measured in each leg (in the posterior tibial artery) using a random zero sphygmomanometer and a Sonicaid Doppler probe. Finally, in the reactive hyperaemia test which followed, ankle systolic blood pressure was assessed in each leg 15 seconds after the release of a cuff occluding arterial flow just above the knee for four minutes at approximately 50 mm Hg above systolic blood pressure. An electronic timer was used for standardising the timing of the procedure. Subjects not known to have diabetes underwent an oral glucose tolerance test (GTT) whereby a blood sample was analysed for circulating glucose levels before and 2 hours after an oral administration of a glucose load, consisting of 335 mL Solripe Gluctoza Health Drink containing 75 g of glucose (Strathmore Mineral Water Company).

4.3. THE EDINBURGH ARTERY STUDY: FIVE-YEAR FOLLOW-UP EXAMINATION

Approximately five years after the baseline clinical examination in 1987/8, all surviving and eligible subjects (and still residing in Edinburgh City) were invited to attend a follow-up clinical examination. The procedures of the five-year follow-up examination are detailed below.

4.3.1. Invitation to Study

Each subject was sent an invitation letter and offered either to come to the study clinic or have the medical procedures performed at home. All travel expenses incurred were fully reimbursed, and subjects who lived outside the City of Edinburgh were offered overnight accommodation but not a home visit. Subjects who did not attend the clinic, missed their appointment, or did not respond to three letters of invitation, were sent a self-administered questionnaire to fill in (the same was administered to clinic attenders). Those not returning the questionnaire were telephoned in the first instance, then visited at home and asked to complete it. Participants whose invitation letter was returned by the post office were traced through the Primary Care Division of Lothian Health Board, and the invitation procedure repeated.

4.3.2. Clinical Examination

Medical examinations were carried out by a team of three specially trained nurses between November 1992 and March 1994. Before the clinical procedures were performed, subjects completed a self-administered questionnaire which was comprised of, in addition to the annual questions about cardiovascular events, questions concerning sociodemographic characteristics, smoking history, medications (including aspirin), age at menopause, and the WHO angina and intermittent claudication questionnaire (Rose, 1962).

After a rest of five minutes, systolic and diastolic blood pressure was measured in the right arm using a Hawksley random zero sphygmomanometer. In each leg, the femoral, posterior tibial, and dorsalis pedis arteries were palpated for peripheral pulses. Ankle systolic blood pressure was assessed using a Sonicaid Doppler ultrasound probe. Standing height was measured to the nearest 5 mm without shoes, using a free-standing metal ruler on a heavy base, while weight was measured to the nearest 100 g on a digital Soehnle scale. The above measurements were made using the same equipment that was used in the baseline clinical examination.

Carotid artery scanning was carried out using an ATL UM9, HDI Duplex Scanner. The carotid arteries were first examined in a transverse plane and then longitudinally. The following arterial sites were examined bilaterally: the internal carotid artery, the external carotid artery, the common carotid artery, and bulb. An assessment of the intima-media thickness was made at the far wall of the common carotid artery, 2 cm proximal to the arterial bifurcation. All scan images were videotaped and those in which measurements were not made but suggested significant disease were reviewed by a consultant radiologist and a member of the study team. A decision was then made as to whether the subject should be re-examined by the consultant.

An ECG was taken from each participant using a Hewlett Packard 12 lead portable 'pagewriter' and later on coded independently by two raters using the Minnesota code system (Prineas et al., 1982). In the event of a non-agreement between the two coders, the ECGs were read over by a consultant cardiologist who made the final decision. Lastly, a sample of 30 ml of venous blood was taken and stored for a subsequent examination of haemostatic, rheological, and genetic factors.

4.4. THE EDINBURGH ARTERY STUDY: TWELVE-YEAR FOLLOW-UP EXAMINATION

A second follow-up clinical examination was held in 1999 (12-year follow-up) to which all eligible subjects were invited. The recruitment procedures and the methods of the clinical examination are discussed below.

4.4.1. Invitation to Study

All eligible EAS subjects (alive at the time of testing, still willing to participate, and had not been excluded by their GPs) were invited to the follow-up examination. Invitation letters were sent by post and subjects offered to come to a study clinic or to be seen at home. All travel expenses incurred were fully reimbursed. Subjects residing outside the City of Edinburgh were offered an overnight accommodation. Subjects not responding to the first invitation letter were telephoned and offered another appointment. Non-contactable subjects were sent a second letter of invitation, and a questionnaire (see below) was mailed out to all non-responders. Subjects whose invitation letter was returned by the post office were re-invited after the Primary Care Division of Lothian Health Board was contacted for the subject's new place of residence.

4.4.2. Clinical Examination

Comprehensive clinical examinations were held during 1999 and testing was carried out by a team of three staff: a research fellow, a physiological technician, and a nurse. Before undergoing physical testing, all subjects were asked to complete a questionnaire enquiring about personal characteristics, angina, intermittent claudication and previous MI, in addition to smoking history, and respiratory symptoms.

Height was measured without shoes to the nearest 5 mm using a stadiometer: weight was measured without outer clothing to the nearest 100 g using a digital scale (Soehnle). After a few minutes rest, systolic and diastolic blood pressure was taken in the right arm using a Hawksley random zero sphygmomanometer. In each leg, peripheral pulses were palpated and ankle systolic blood pressure was measured using a Sonicaid Doppler ultrasound probe. All measurements were made using the same equipment that was used at the previous clinical examinations.

Scanning of the carotid arteries was performed using an ATL UM9, HDI Duplex Scanner. The following arterial sites were inspected, first in a transverse plane and then longitudinally: internal and external carotid arteries, common carotid artery, and bulb. An assessment of IMT was made at the far wall of the common carotid artery, 2 cm proximal to the arterial bifurcation. In addition, estimation was made of both peak systolic velocity and plaque size. All scan images were videotaped, and those suggesting disease but in which no measurements were made, were reviewed by specialized members of the study team.

The diameter of the abdominal aorta was measured by ultrasound scan using a 3 MHz transducer and an ATL UM9, HDI system. The maximum of three readings was taken as the diameter. For a few subjects unable to attend the clinic, an Aloka 500 portable scanner was used on a visit to their home.

A 12 lead ECG was taken from each subject using a Hewlett Packard portable 'pagewriter' and later coded by two raters according to the Minnesota code system (Prineas et al., 1982). A consultant cardiologist was consulted in the event of non-agreement by the two raters. Finally, a 20 ml venous blood sample was drawn from each subject without tourniquet, centrifuged and aliquots of citrated plasma stored at -40 °C.

4.5. IDENTIFICATION OF CARDIOVASCULAR EVENTS

Every effort was made to ensure the detection of new (incident) fatal and non-fatal cardiovascular disease events in the EAS cohort during follow-up. Information on the development of new events was obtained from a number of different sources. These, and the methods used in locating EAS subjects in relevant health records, are described in the following sections.

4.5.1. Non-Fatal Events: General Practitioners

At the beginning of the EAS, all general practices participating in the study were visited and permission was granted to flag relevant patient records with plastic envelopes containing pink cards and prepaid envelopes. A pink card containing subjects' details (name, address, city of residence, patient study number, date of birth, and general practice code number) was attached to the front of patients' GP records to be returned following a cardiovascular event. General practitioners were provided with new cards and envelopes to replace the ones sent. The pink card was also returned in the event of patients changing an address or a GP, in which case they were traced through the Lothian Health Primary Care Division.

4.5.2. Non-Fatal Events: Information and Statistics Division of the Scottish Office Home and Health Department

Annual computer printouts of all hospital discharges occurring for subjects in Scotland for the previous year were provided by the Information and Statistics Division (ISD). First, a list with all discharges with the following ICD-9 codes was provided: 410-414; 430-438; 440-444; 785; 250.6; 342, 344.3, 344.4; 781.2, 781.4; 784.3, 784.5; 798, 798.1, 798.2, and 798.9. The list was then checked to identify EAS subjects. Following a systems change in 1991 it became possible to link the EAS participant list to the database of hospital discharges. All subsequent lists were classified by subject's name rather than by ICD code. These were matched with the ISD file on name, date of birth, sex, and study members. In the former system, once subjects were identified, their records were obtained at the relevant hospital and checked for details regarding admission and progress. An event was recorded only if study criteria were met. Under the latter system, discharges with relevant ICD codes were identified and followed up at the hospital. Hospital records were reviewed and events noted if study criteria were fulfilled.

4.5.3. Non-Fatal Events: The Royal Infirmary of Edinburgh

Lists with information on new referrals to the peripheral vascular clinic with relevant ICD codes were supplied by the Royal Infirmary of Edinburgh. In addition, a list of vascular operations, coded using a coding system for surgical operations developed by the Surgical Audit Committee, was provided. The lists were read over by the study coordinator who identified EAS subjects and appropriate follow up of medical records was carried out as required.

4.5.4. Non-Fatal Events: Annual Questionnaires

Each participant in the study was sent an annual questionnaire enquiring about the development of the following conditions in the previous year: heart attack, stroke, chest and leg pain, loss of power in arms or legs, and hardening of arteries. Participants were also asked about any hospital attendances or visits to a GP. Those who answered positively to any of the above, or were unsure in their reply, were followed up with the WHO angina and intermittent claudication questionnaire which they were asked to complete and return in a prepaid envelope. If the participants had consulted their GP for any of the above, the GP was sent a short questionnaire to fill in, in order to clarify the diagnosis. In the event of a hospital attendance or admission, medical records were examined to determine whether study criteria for the event were fulfilled.

4.5.5. Fatal Events: United Kingdom National Health Service Central Registry

Each participant's record at the National Health Service Central Registry (NHSCR) was flagged in order to ensure that death certificates would be automatically forwarded for all study participants dying in the United Kingdom. In addition, cases of mortality from cardiovascular causes were further examined using hospital or GP records in order to determine that the study protocol criteria were appropriately fulfilled.

4.6. METHODS OF COGNITIVE FUNCTION TESTING

4.6.1. First Round of Cognitive Function Testing

The 'Cognitive Function Project' of the EAS was launched with the first round of cognitive function testing in 1998/9. A range of cognitive abilities was assessed in the study subjects attending cognitive function testing. The results from the first round of cognitive testing are described below while a more detailed discussion on the subject recruitment, the procedures of cognitive testing, and the cognitive test battery that was used on both occasions is provided in the subsection on the second round of cognitive testing.

Subject Recruitment

Over the 11 years since the baseline examination in 1987/8, approximately 380 study subjects were reported to have died. Inevitably, this left 1209 subjects available for cognitive testing. Further reductions in the number of subjects eligible for participation resulted from 61 withdrawals from the EAS, reports of 19 additional deaths occurring during the one-year study period, and 28 exclusions made by GPs. In total, 1103 subjects were sent a letter of invitation to attend cognitive function testing. Of these, 933 (84.5%) replied to the invitation, while 151 (13.7%) subjects did not reply, and 19 (1.7%) letters were returned by the post. Of those who replied to the invitation letter, 740 (67.0%) accepted the invitation while 193 (17.4%) subjects declined. Of the 740 subjects who accepted to be tested, 717 attended testing, 22 did not attend, and one subject refused consent when visited at home. Complete data on at least one cognitive function measure are available for 698 (97.3%) out of the 717 subjects who attended cognitive testing.

Cognitive Testing Procedures

The cognitive function testing, which began in March 1998 and was completed in April 1999, was carried out by two trained members of staff (a research nurse and a psychologist). Approximately two-thirds of the subjects attended a University clinic, while the remaining one-third was tested at home.

4.6.2. Second Round of Cognitive Function Testing: Subject Recruitment

The recruitment of EAS subjects to follow-up cognitive testing (second round) began in early July 2002. Subjects who had participated in the first round of cognitive testing in 1998/9 were potentially eligible for participation in the study. The procedures used in selecting and inviting subjects to the study are described below. Documents relating to the recruitment of subjects are provided in appendices C-1 through C-4.

Eligibility for Participation

All subjects who had undergone cognitive testing in 1998/9 were considered as potential candidates for participation in the study. However, recruitment of subjects, whose compromised physical or mental health status (for example, sight or hearing problems, or dementia) might have limited their capability to undergo cognitive testing, was discouraged. All general practices (letters were addressed to a contact GP in each practice) were sent a complete list with the names of subjects to be recruited from the respective practice by the study team, which was to be notified about anyone considered unfit to participate for any of the reasons above. As a result, all surviving subjects, whose participation in the cognitive testing was approved of by their GPs, were considered eligible to take part in the study.

In the instance where a subject had moved and registered with a new general practice (information supplied by a contact GP in response to the letter sent for the purpose described above) the subject's new address was requested from the previous practice. In response, a letter with the subject's name and date of birth was sent to the manager in charge of the practice the subject was currently registered with. In the letter the study team requested a permission to approach the subject and anyone deemed unsuitable to participate in the cognitive testing for health reasons or otherwise, was excluded from participation. On the rare occasion when the previous general practice was unable to provide the study team with data on the subject's new place of residence, Lothian Health Board was able to provide the necessary information. No further attempts were made in order to obtain information on new addresses if the above routes available to the study team proved unsuccessful.

Invitation to Participate

Letters of invitation to participate in the second round of cognitive function testing were mailed to all eligible EAS subjects. The subject invitation letter had enclosed an information sheet describing the purpose of the study, a reply slip which also requested the subject's current contact details, and a pre-paid envelope. Those willing to participate in the study were given the option to be cognitively tested at a University of Edinburgh clinic or at home. Subjects were allowed approximately 3-4 weeks to reply to the initial invitation letter before they were re-contacted by the study team.

Subjects who answered positively (ticking the 'yes' box on the reply slip) to the initial invitation letter were contacted by phone shortly after the study team received their reply form. Those to be tested at the University clinic were given an appointment through the phone and subsequently mailed a reminder and a map of the University clinic and surrounding area. Subjects requesting a home visit were only given a date to be tested by phone. In the case where a subject did not have a phone, but had expressed a willingness to participate, a letter with a provisional appointment was sent out. Subjects replying 'yes' to the first invitation letter but wishing not to take part when subsequently contacted by phone were asked if they could be re-contacted at a later date in case their personal circumstances might change. Those subjects who were willing to undergo testing but could then not be reached by phone (no answer or answering machine constantly connected) were repeatedly phoned at different days and hours. If, despite repeated attempts, there was still no answer, a letter with a pre-arranged appointment at the University clinic and a map was mailed to the subjects. Subjects not turning up at the clinic for their provisional appointment were categorised as 'non-responders'.

All subjects rejecting the invitation (ticking the 'no' box on the reply slip) to cognitive testing were given a second opportunity to participate in the study in case they had changed their mind about taking part. At a later date a second invitation letter was mailed out, and while subjects who accepted the invitation were given an appointment, no further attempts were made to recruit those still refusing to undergo testing (categorised as 'refusal to participation').

Any subject not replying to the first invitation was followed up with a second copy of the invitation letter. Depending on the type of response to the second invitation, either an appointment was made or subjects were classified as 'non-responders' or those who refused participation. However, subjects not responding to the second invitation were labelled as 'non-repliers'.

4.6.3. Second Round of Cognitive Function Testing: Cognitive Testing Procedures

The follow-up phase of the cognitive function testing took place from September 2002 to December 2003. The following sections describe in detail the settings of the testing and the specific measures taken in order to ensure the quality of the cognitive test data.

Training of Investigators

Before the initiation of the cognitive function testing, an appropriate training in the administration of cognitive function tests was provided to the study team. The two investigators who carried out the testing were informed about the basic cognitive test procedures by two senior members of academic staff (psychology consultants on the EAS) from the Department of Psychology at the University of Edinburgh. Subsequently, one of the investigators was trained to the necessary level for testing through practice on fellow co-workers and then on study subjects attending the University clinic. The second investigator was then trained by the first by sitting in on several clinic test sessions and monitoring the process of test administration. After several sessions, the second investigator applied the tests with either the first investigator or a study psychologist monitoring the performance. Any issues or problems regarding the administration of the tests arising during the training sessions or at any point during the cognitive testing were thoroughly discussed and led to conclusion within the study team.

Cognitive Function Testing Sessions

Subjects either attended a University clinic for cognitive function testing or were visited at home. Testing at the clinic was carried out in a moderately warm, quiet and well-lit room in the Department of Public Health Sciences at the Edinburgh University Medical School. Subjects attending the clinic were usually tested between 10:00 am and 4:00 pm during normal working days. All travel expenses (including parking cost) were fully reimbursed. Subjects seen at home were normally tested between 10:30 am and 3:00 pm, Monday through Friday.

Inter-Rater Consistency in Cognitive Function Test Administration

In order to ensure consistency in the administration and scoring of the cognitive function tests, a 'quality control' exercise was carried out during the period from January 13 to May 23 2003. The procedure involved the two investigators undertaking 15 duplicate cognitive function test sessions in which one or the other would carry out the testing while the second investigator simultaneously observed and scored the cognitive test battery. In this way, both investigators registered the subject's answers (item by item) on each of the following cognitive measures (see next section for description of individual cognitive tests): The Mini-Mental State Examination; The National Adult Reading Test; The Logical Memory Test (Immediate and Delayed); The Verbal Fluency Test (letters C, F, and L). Since both the Ravens Progressive Matrices and the Digit Symbol Test require the subject to fill in a standard scoring sheet (tick boxes), they were not scored simultaneously by the two investigators as the verbal tests were. Rather, after each session, the answering forms for these two tests were photocopied and scored individually by the investigators (see appendix D). Any discrepancies relating to the administration and marking of the cognitive function test battery (or any aspect of it) were properly addressed by the study team.

4.6.4. Second Round of Cognitive Function Testing: Cognitive Function Test Battery

The cognitive function test battery used in the first and second rounds of testing in the EAS was comprised of six neuropsychological tests, a test assessing subjects' pre-morbid ability and a scale aimed at determining anxiety and depression levels. The test administration time was approximately one hour. The individual components of the test battery are described below in the order they were presented to the participants. Copies of each of these are supplied in secions 1 to 9 of Appendix D.

Consent Form

In line with ethical rules, the study subjects agreed to participate in the cognitive testing by signing a consent form after having been made clear that they could withdraw from the study at any time without giving a reason, that such a decision would in no way affect their standing with their GP, and that personally they would derive no direct benefit from the study. Also, participants were offered to read over the subject information sheet (had they not brought with them the copy mailed out to them accompanying the invitation letter) and encouraged to ask questions and discuss the study before signing the consent form.

Medical Questionnaire

In order to rule out any physical medical conditions interfering with subjects' performance on the cognitive tests, a medical questionnaire was administered. In a dichotomous manner, the subjects were asked whether or not they suffered, or had ever suffered, from any of several conditions, such as Parkinson's disease, stroke, sensory problems, arthritis, or were on any medications at the time of testing.

The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a brief self-administered instrument designed for detecting mood disorder in non-psychiatric patients, and has also been found to be a valid measure of the severity of both anxiety and depression (Zigmond and Snaith, 1983).

The HADS consists of two sub-scales that reflect subjects' anxiety and depression levels over the past few days before completing the scale (examinees were encouraged to note down their immediate reaction to each item rather than taking too long time to think about what to reply). Each sub-scale is comprised of 7 items or statements that are based solely on the psychic symptoms of anxiety and depression (items relating to both physical and emotional disorder e.g. dizziness or headaches are not included). Each item is rated on a four-point scale (0-3) and the highest total score on both scales is 21. Non-cases and possible cases fall into the range 0-7 and 8-10, while a total score of 11 or more indicates a probable case (the HADS has good sensitivity and specificity for determining whether a particular patient is probably a psychiatric case of anxiety or depression although it does not allow a definite diagnoses, and only gives a dimensional rather than a categorical representation of mood (Herrmann, 1996)).

The Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a brief cognitive measure that is widely used for evaluation of a restricted set of cognitive functions in both clinical practice and research (Folstein et al., 1975).

The MMSE is comprised of 20 questions and tasks that fall into the following domains: orientation-time, orientation-place, memory-registration, attention and calculation, memory-recall, praxis-ideational, praxis-copying and drawing, and spontaneous praxis-writing. As an example of a question from the orientation-time domain, the examinee is asked to tell the examiner what time it is in terms of day, month and year at the time of testing, while in the attention-calculation domain, the subject is asked to spell the word 'world' backwards. Before administering the

MMSE, examinees were told that they were going to be asked a series of relatively simple questions about the day they had their test, about their location and so on. One point is awarded for each correct answer and the points of correctly answered questions are summed for each domain. The maximum score obtainable on the test is 30 (range 0-30).

The National Adult Reading Test

The National Adult Reading Test (NART) is a briefly administered reading test which is frequently encountered in both clinical and research settings as a measure of pre-morbid intellectual ability (Nelson and Willison, 1991). The NART is comprised of a list of 50 single words that are irregular with respect to common rules of pronunciation in order to minimise the possibility of reading by lexical decoding rather than word recognition. The word order on the list is of graded difficulty and the test is assumed to make minimal demands on current cognitive abilities because it only requires the examinee to read out loud one short single word at a time. Among the words included in the NART test are ache, nausea, radix, and beatify.

The number of correctly and incorrectly pronounced words is noted by the examiner as the test progresses. Slight variations in pronunciation are allowed when these are due to regional accents. Overall, however, the accuracy of the scoring of the NART depends solely on the examiner's accuracy in interpreting the examinee's responses and his/her adherence to the appropriate pronunciation of the words as set out by the test instructions (both in print and audio format). A maximum score of 50 (range 0-50) indicates all words correctly pronounced.

The Wechsler Memory Scale-Revised: Logical Memory Test (Immediate Recall)

The Wechsler Memory Scale-Revised (WMS-R) is a revised version of the Wechsler Memory Scale which is a widely used clinical instrument designed for evaluation of major dimensions of memory functions in adolescents and adults (Wechsler, 1987). The test is both used as a diagnostic and screening tool for use as a part of a general neuropsychological examination or a clinical examination where assessment of memory functions is required.

The Logical Memory (LMT) test is one of eight sub-test of the WMS-R test battery and assesses immediate or short-term memory for verbal material. The test is comprised of two short stories (A and B) of almost equal difficulty that are read to the examinee. The examinee is told to pay a close attention to the two stories and the words they use, and after hearing each story, asked to retell the two stories to the examiner. The examinee is given one point for every idea of the story correctly recalled and the points are summed for each story. The total score is comprised of the total ideas produced for both stories.

The Raven's Standard Progressive Matrices

The Raven's Standard Progressive Matrices (RPM) constitute a measure of eductive or non-verbal ability which refers to the process of educing new insights and information out of that which is perceived or already known by the individual (Raven et al., 1977). More specifically, the RPM set out to measure a person's ability to make sense of complex situations and identify relationships between apparently unrelated structures. The processes underlying this sort of cognitive ability have been described as being largely non-verbal, depending on flashes of insight too rapid for assimilation into language.

The RPM comprises 60 items grouped in five sets (12 in each set). Each item contains a pattern problem where a part or a piece has been removed and six to eight pictured inserts of which only one contains the correct pattern. The examinee is asked to identify the piece that correctly completes the pattern and write the number of the piece they choose on an answer sheet. Items increase in difficulty across each of the five sets (item one least demanding, item 12 most demanding), and between sets (set A least demanding, set E most demanding). One point is given for each correct answer and the maximum score given for each of the five sets is 12. The maximum test score is 60 (range 0-60). In the EAS, examinees were given 20 minutes to complete the test after having had a short practice trial involving the first three test items.

The Lexical Verbal Fluency Test

The Lexical Verbal Fluency Test (VFT) is based on the quantity of words produced orally by an individual in response to a stimulus (letter of the alphabet) within given time limits (Lezak, 1995). Neural imaging studies, and studies of brain lesions, have demonstrated how lexical fluency tasks seem to place a high demand on strategic search processes (divergent thinking) involving specific regions of the left and right frontal lobes.

The VFT test consists of three one-minute word-naming trials. Examinees are asked to name as many words as they can think of beginning with a particular letter of the alphabet (the letters C, F, and L were used in the EAS). The total score is based on the total number of acceptable words produced. The letters are chosen on the basis of the frequency of English words beginning with these letters. Thus, words beginning with the letter C have relatively high frequency, while the frequency of words beginning with the letter F is relatively lower, and words beginning with L have still lower frequency. Names of persons and places (proper nouns), numbers and the same words with different suffices (e.g. sing and singing) are not allowed, and in order to familiarize the examinee with the task a practice trial involving the high frequency letter 'S' is provided. The examinee is expected to provide two or three words beginning with the letter 'S' before moving on to the timed trials.

The Wechsler Adult Intelligence Scale-Revised: The Digit Symbol-Coding Test

The Digit Symbol-Coding Test (DST), a measure of psychomotor performance, is one of several subtests of the Wechsler Adult Intelligence Scale (WAIS-R) which is a clinical instrument designed for evaluating the intellectual ability of adults 16 to 89 years of age (Wechsler, 1981).

The DST is composed of four rows containing 100 blank boxes, each paired with a number from one to nine that have been randomly ordered. Above these rows is a key that pairs each number with a unique symbol. Before doing the actual test, the examinee briefly practices on the first seven boxes which do not count towards the final score. The main test requires the examinee to fill in as many blank boxes with the corresponding symbols as possible in 90 seconds (the examinee is closely monitored during the testing and a stopwatch is used for time taking). The final test score is based on how many boxes the examinee correctly managed to fill in within the given time limits. The maximum score obtainable is 93.

Wechsler Memory Scale-Revised: Logical Memory Test (Delayed Recall)

Following an approximately 25-30 minutes delay since the two stories (A and B) were read to them, examinees are prompted to recall the stories and tell the examiner everything they can remember about them (a process called 'delayed recall' which denotes the examinee's ability to retrieve stored verbal material from long-term memory) (Wechsler, 1987). In the instance where examinees have no recollection of the two stories whatsoever, a brief reminder of the stories is read to them in order to enable retrieval from memory.

4.7. DATA HANDLING AND ANALYSIS

4.7.1. Entry of Cognitive Data

Data from the second round of cognitive function testing were entered into a computer using EpiData, a software package which has proved to be compatible with a number of statistical programmes (Lauritsen et al., 2001). Data entry (undertaken by the author) commenced on January 20 2004 and finished on January 28 2004. The data entry was repeated by a departmental technician who began the data entry on January 29 2004 and completed the task on February 6 2004. The two independent data files thus generated were then compared with regard to each of the 22 numerical variables for each patient using the 'Validate Duplicate Files' command of the EpiData software which resulted in flagging of any non-matching records. In the event of non-matching records, the original paper questionnaires were consulted, and any discrepancies arising during the data entry process were corrected.

4.7.2. Data Handling and Variable Computation

The cognitive data set from the second round of cognitive testing was exported from EpiData into SPSS version 12.0 which was used for statistical description and analysis (SPSS, 2004). Study numbers (a unique five digit number assigned to each patient) were used to match the cognitive data set with data collected previously from the baseline examination and during follow-up.

The complete data set was inspected for errors (for example, values outside the possible range for a given variable) and missing values. In the case of missing values on the cognitive tests, the original paper questionnaires were consulted and checked with regard to whether study subjects had left out individual items (and the corresponding test scored as missing) or refrained from doing the test. This resulted in re-scoring of several more tests leading to an increase in the number of valid cases for analysis. Further investigation of the data showed no consistent pattern with regard to missing values on the cognitive tests. For instance, having missing data (any missing versus none) was not related to having cardiovascular disease, nor was having missing data on any particular cognitive outcome.

Cardiovascular Disease Categories

As previously described, extensive information on the prevalence and incidence of CVDs has been amassed following the baseline examination in 1987/8. Moreover, a number of different sources were used in order to ascertain the occurrence of new cardiovascular events. A diagnosis of CVD was assigned to those subjects found to meet predetermined study criteria at baseline or any time during follow-up (see appendix E for diagnostic criteria). A cut-off date for diagnosis of CVD was set at six months prior to the beginning of the second round of cognitive function testing. This was decided mainly in order to minimise the possibility of including in our analyses those subjects, if any, who might have been suffering from acute post-CVD confusional state or sensory-motor deficits when cognitively tested in 2002/3. Also, since a major objective of the current study was to examine CVD in relation to change in cognitive performance between two test occasions, separated by four years, a decision was taken to have the cut-off date prior to the second rather than the first round of mental testing.

The data collected at each of the three clinical examinations were stored in a central database. An event file containing information from the continuous follow-up (based on annual questionnaires, flagging of GP records, and hospital discharge records) was matched with the central data base using patient study numbers. Inspection of the combined data set revealed a number of duplicate events indicating an overlap between the different sources of data. In one instance, intermittent claudication noted at the five-year follow-up examination had been entered in the event file a year earlier (reported in an annual questionnaire). As a result, the respective date of diagnosis was identified for each subject reporting a major cardiovascular event at any time over the study period. Then, the earliest date was chosen for those subjects who had dates for both non-fatal events and dates from either of the two follow-up clinical examinations. In the case of multiple events of the same type, the earliest event based on the date it was first reported was taken as the index event.

For the purpose of the present investigation, a major objective of which was to examine cognitive outcomes in relation to different clinical manifestations of atherosclerotic disease, the following six CVD exposure groups were created: any CVD with the exclusion of subjects with stroke, angina pectoris, intermittent claudication, MI, stroke, and a single comparison group comprising subjects considered free of CVD since they did not meet the study criteria for any of the above vascular conditions during the study period. Assignment to any of the CVD groups was based on the presence of the most severe manifestation of atherosclerotic disease noted for each case, yet acknowledging the co-existence of multiple events in a substantial number of subjects ever reporting symptomatic CVD. In the light of this, and with regard to the total number of cases available for each CVD category among those who underwent cognitive assessment in 2002/3, a considerable overlap between some CVD exposure groups was inevitable. An exception was the category for subjects with angina, which was kept distinct from that of more severe CVD conditions, such as intermittent claudication and stroke, allowing the study of cognitive function in relation to a relatively mild, non-acute form of atherosclerotic CVD.

Cognitive Outcomes

Given the high correlation (r=0.89 for the 1998/9 data and r=0.92 for the 2002/3 data) between the immediate and delayed components of the LMT (these are essentially based on the same test material) they were combined to form a total LMT score which was used in all statistical analyses. Moreover, the letters 'C', 'F', and 'L' of the VFT were combined into one test score representing the total number of words produced. Again, the total score was used throughout.

In order to compute a general cognitive factor representing the variance common to all the cognitive tests, the following measures were subjected to a principal components analysis (PCA): LMT (immediate and delayed recall combined), RPM, VFT (all three letters combined), and DST. The data were found to adequately meet the necessary criteria for PCA (the sample size was substantially greater than the necessary minimum; factorability of the correlation matrix measure of sampling adequacy and Bartlett's test of sphericity indicated the adequacy of the intercorrelations amongst the cognitive outcomes; scatter plots of all cognitive outcome combinations revealed no non-linear relationships; the data did not violate the assumptions regarding no outliers). Scores were saved on the first unrotated principal component. Each cognitive test loaded strongly on this component which accounted for 57.1% of the variance, thus validating the use of a general factor (a scree plot was also inspected in order to confirm the results from the PCA factor extraction).

In addition, given the high loading of each of the tests on the general factor, further outcome variables were computed in order to examine any non-general factor cognitive elements associated with CVD. This was carried out using multiple linear regression whereby each of the cognitive tests (LMT, RPM, VFT, and DST) were regressed on the general cognitive factor each at a time. The new outcome variables comprised the general factor-adjusted standardised residuals for each cognitive test.

Putative Confounding Variables

The following variables, based on their associations with both CVD and cognitive outcomes, were considered as possible confounders in the current study: 1) Age at the time of cognitive testing in 2002/3 and sex; 2) Baseline level of education which was categorised as a four-level variable (university, post school training, secondary, primary); 3) Baseline level of occupational social class which was grouped as a five-level variable (social class IV and V were combined; 4) Mood levels at the time of cognitive assessment in 2002/3 as assessed by the HADS scale; 5) Prior cognitive ability level, which was based either on the actual cognitive test scores in 1998/9 or estimated using the NART; 6) Baseline (in 1987/8) levels of smoking, alcohol intake, and physical activity. Pack-years of smoking were estimated by multiplying the number of 20-cigarette packs smoked per day with the number of years as a smoker. A zero value was entered for life-long non-smokers. Alcohol intake was based on the number of alcohol units consumed in a typical week at baseline. Physical activity was grouped into four levels of intensity according to type of activity (ranging from none to strenuous); 7) Baseline body mass index was defined as weight in kilograms divided by the square of the height in meters; 8) Diabetes at baseline was based on subject's recall of doctor's diagnosis of diabetes, current treatment for diabetes, or 2-hour blood glucose concentration equal or greater than 11.1 mmol/L. Glucose levels ranging from 7.8-11.0 mmol/L were used to denote impaired glucose tolerance; 9) DBP and SBP at baseline; 10) Baseline serum levels of total, LDL, and HDL cholesterol, and serum triglyceride levels; 11) Plasma homocysteine levels measured at the five-year clinical examination; 12) Baseline levels of circulating markers of inflammation and haemostasis, and baseline indicators of blood rheology; 13) Place of cognitive testing (clinic versus home).

4.7.3. Data Description and Bivariate Statistical Analysis

Each of the CVD groups, cognitive outcomes, and potential confounders were examined and described. Categorical variables were described with regard to the frequency (percentage/number) at each level of the variable. The distribution of continuous variables was explored using both statistics (the mean and standard deviation) and visually inspecting histograms. Any outliers were checked and corrected if necessary. Distributions of all continuous variables apart from the following approximated normality: the HADS anxiety and depression scores, total units of alcohol, pack-years of smoking, serum lipoprotein levels, and levels of serum CRP and IL-6. Therefore, for descriptive purposes, the median and the interquartile range of each of these factors were used. Statistical transformations were also carried out and used in all multivariate analyses. A square root transformation of the raw values of pack-years of smoking was performed and the HADS anxiety and depression scores were transformed using the logarithm of n+1 scores in order to avoid the logarithmic transformation of a score of zero. The logarithmically transformed form of the remaining variables above was used in all subsequent analyses.

Bivariate analyses preceded testing specific hypotheses using multivariate methods. Rank correlations amongst cognitive tests were computed, first by using the data from the first and second rounds of cognitive testing separately, and then by calculating the correlations between the two data sets. Pearson's r correlation coefficients were calculated for each pair of linear correlations in order to estimate both the direction and the strength of the relationship between any two variables. Scatter plots were also produced and visually inspected for linearity. Levels of CVD risk factors were compared bivariately in subjects with and without CVD. The statistical significance of differences in categorical CVD risk factors was determined using the Chi-square test (Chi-square test for trend in the case of ordinal variables). Differences in median levels of risk factors by cardiovascular disease status were assessed using the Mann-Whitney U Test. Moreover, mean levels of each cognitive function test variable and other normally distributed CVD risk factors were compared using the t-test after ensuring assumptions concerning the normality of the distribution and homogeneity of the variance were met. Lastly, the general cognitive factor scores were not included in the examination of the four-year change in mean cognitive test scores since the general factor represents a standardised variable, with a mean of zero and standard deviation of one on each occasion of cognitive testing. However, the general factor scores are valuable when it comes to examining the contributions to individual differences. Therefore, it was employed as a dependent variable in the multivariate analyses which are described next.

4.7.4. Multivariate Statistical Analysis

Analysis of covariance (ANCOVA) was applied for assessing the statistical significance of any mean differences in both general cognitive function and specific mental functions among subjects with and without CVD while adjusting for potential confounding factors (see below). Multiple linear regression analysis was used for examining the independent contribution of CVD and any vascular risk factors to change in general and domain-specific cognitive abilities while adjusting for possible confounders. In a further set of examinations, the multiple linear regression-based analyses above were repeated using the general cognitive factor-adjusted standardised residuals of each cognitive test as dependent variable.

In the modelling approach used (the same method was applied in both the ANCOVA and multiple linear regression analyses), potential confounding variables were introduced into the models in three cumulative steps. In the first, age and sex were controlled for. Then, in subsequent steps, two different types of adjustment were made for prior mental ability level. In one set of models, the 1998/9 performance score for the respective dependent cognitive variable in 2002/3 was used as a covariable. This adjustment for earlier test performance allowed determining the level of actual change in specific cognitive abilities in relation to CVD over a time frame of approximately four years. In another set of models, peak prior cognitive ability as indexed by the NART was used as a covariable. By controlling for a well-validated estimate of peak ability, it was possible to assess the impact of vascular disease on the imputed decline from best-ever level of cognitive function to that actually measured here in old age (in 2002/3) (Deary et al., 2004). Using regression in this way with prior scores as covariables is considered superior to using change scores; for example, it prevents the spurious correlation between the baseline and change scores found (Campbell and Kenny, 1999).

Further adjustment for potential confounding by vascular risk factors was made for those variables only, which in unadjusted comparisons, differed significantly between subjects with and without CVD. These were incorporated into the age, sex, and cognitive ability-adjusted models each at a time. The most distal factors on the hypothesised causal pathway were added first and then all other factors (Victoria et al., 1997). Only those confounders which exerted independent effects in the age, sex, and cognitive ability-adjusted multiple linear regression models were retained for further analyses, which were based on examining their individual and cumulative effects on the cognitive outcomes, as well as the effects of their control on the association between CVD and cognitive change.

Prior to the above analyses, the data were checked with regard to whether basic assumptions for using multiple linear regression methods were met (the sample size was considered to be adequate; an inspection of a correlation matrix demonstrated that none of the variables were too highly correlated ($r>0.9$); none of the variables constituted a combination of other independent variables; the data were visually inspected for outliers as a part of the univariate description of the data; standardised residual scatter plots were visually inspected for violations of normality, linearity, and homoscedasticity.

A statistical power analysis was conducted using nQuery version 4.0 on the sample of survivors participating in the follow-up cognitive function testing in 2002/3. In one sample calculation, the following conditions were applied: α (two-tailed significance level)=0.05, n=279 (the average effective sample size available for the regression analyses) and the inclusion of three covariates (age, sex, and prior cognitive ability) which, on average, accounted for approximately 45.0% of the total variance in the outcome variable (R^2=0.45) in the multiple linear regression analyses. Based on the above, the results from the analysis demonstrated 80% statistical power for detecting an increase of 0.015 in R^2 following the addition of a further covariate to the model (i.e. there was adequate power for detecting relatively small effects that any additional predictor variables might have exert when added to the core model.

4.8. CHAPTER SUMMARY

The aim of the present chapter was to describe the methods of the EAS and the spectrum of data which have been gathered from baseline onwards through more than a decade of follow-up. More specifically, a major goal of the text was to provide a detailed discussion of the routes taken in the collection and analysis of data on cognitive outcomes and CVD for meeting the particular objectives of the current study. As highlighted earlier, the EAS may be considered well suited for addressing some of the fundamental shortcomings of prior reports examining the relationship under study, given it is based on a random sample from the elderly general population, and has collected longitudinal data on different cognitive abilities, information on both prevalent and incident vascular disease, and data on a number of possible confounders of the association between CVD and cognition.

CHAPTER FIVE

Study Results

5.1. INTRODUCTION

The present chapter discusses the results from the current study of the relationships between CVDs, vascular risk factors and neuropsychological outcomes in elderly participants in the EAS. In doing so, it first presents results from a sample of subjects who participated in the assessment of cognitive function in 2002/3. This is followed by findings from a comparison of cognitively tested subjects with the total number of survivors as well as subjects eligible for neuropsychological assessment. Subsequently, data on the frequency of non-fatal CVD events, vascular risk factors, and neuropsychological outcomes in 1998/9 and 2002/3 are provided for the cognitively tested sample. Finally, a major goal of the chapter is to report on findings relating to the stated research objectives of the present investigation. These are predominantly based on a series of multivariate analyses which are discussed in the text under separate headings throughout the latter part of the chapter.

5.2. SECOND ROUND OF COGNITIVE FUNCTION TESTING: PARTICIPATION RATES

5.2.1. Number of Eligible Subjects

By mid-year 2002, EAS records revealed that 617 subjects who had provided cognitive data in 1998/9 were still alive and available for recruitment to the second round of cognitive testing. However, as a result of letters mailed out to all general practices (asking about subjects' suitability to take part in cognitive testing) 23 subjects were deemed unfit to participate by their GP for health or personal reasons. Moreover, four more subjects were excluded from participation since they had moved away and neither the general practice nor Lothian Health Board was able to provide the study team with information about their new whereabouts. As a consequence, 590 (95.6%) subjects were deemed eligible to undergo cognitive assessment.

5.2.2. Number of Subjects Invited to Participate

Invitation letters were mailed out to the 590 EAS subjects who had attended cognitive testing in 1998/9, were still alive by mid-year 2002, were considered fit to undergo cognitive testing in 2002/3, and whose address was known to the study team (figure 1). In total, 460 subjects (74.6%) accepted the invitation whereas 114 did not: 101 refused participation and 13 subjects did not reply to two letters of invitation. In addition, 16 deaths occurred over the study period. As a result, 460 subjects were contacted for appointment but before attending cognitive testing, seven subjects withdrew from the study: six refused when asked whether they could be contacted again at a later date and one subject could not be reached despite being telephoned repeatedly at different dates and hours. As a last resort, a letter with a pre-arranged clinic appointment was mailed out to the subject but without success (a reply was never obtained).

In total, 452 (73.3%) subjects attended cognitive testing in 2002/3: 280 (61.9%) were tested at the University clinic and 172 (38.1 %) subjects were tested at home. Of the two investigators performing cognitive testing, the author tested 278 (61.5%) subjects in total, whereas 174 (38.5%) subjects were tested by a senior research fellow in the Department of Public Health Sciences at the University of Edinburgh. Of the 278 subjects tested by the author, 122 were seen at the University clinic (43.5% of all subjects tested at the University) and 156 at home (90.7% of all subjects tested at home).

5.3. COMPARISON OF COGNITIVELY TESTED AND NON-TESTED SUBJECTS

5.3.1. Baseline Cardiovascular Diseases and Sociodemographic Characteristics

Baseline levels of lifestyle and sociodemographic factors, and frequency of CVD, in cognitively tested (n=452) compared to non-tested (n=138) subjects are shown in table 1. The mean age at baseline of tested subjects was 62.6 years compared to 64.0 years of non-tested subjects. Moreover, the proportion of men in the tested group was 49.8% versus 46.4% in the non-tested group. In comparison to non-tested subjects (13.9%), 22.2% of those who were cognitively tested had finished university or some kind of post school training (24.8% versus 12.4%), whereas secondary school was the highest education level completed by 73.0% of non-tested and 51.7% of tested subjects. Approximately 1.3% of tested versus 0.7% of non-tested subjects had completed primary level of education. More tested than non-tested subjects came from social classes I and II (based on current occupation when interviewed at baseline or longest held occupation in the case of retired or unemployed subjects; married women were classified according to husband's occupation). The converse was true for social classes III-VI.

Baseline frequency of both vascular risk factors and disease was compared in cognitively tested and non-tested subjects. For instance, in non-tested subjects, the median level of pack-years of smoking was 10.0, the mean level of systolic blood pressure 144.5, and the percentage of participants with impaired glucose tolerance and diabetes was 19.3 and 3.0% (the tested group had median pack-years of 2.7, mean systolic blood pressure of 138.8, and 9.9 and 2.7% had impaired glucose intolerance or diabetes, respectively). In contrast, body weight (assessed with the body mass index) did not differ between tested and non-tested subjects (25.6 in both groups). Furthermore, with respect to vascular disease, 2.2% of non-tested subjects met baseline criteria for MI and stroke (compared to 2.0 and 1.3% of tested subjects, respectively).

5.3.2. Results from the First Round of Cognitive Testing

Table 2 presents the results from the cognitive assessment performed in 1998/9 among subjects attending or not cognitive testing in 2002/3. For example, the tested group obtained a mean NART score (the mean number of correctly pronounced words) of 33.2 compared to 22.3 in the non-tested group. With regard to specific cognitive outcomes, tested subjects obtained a mean general cognitive factor score of 0.20 whereas the non-tested group obtained a mean score of -0.38 (more than half a standard deviation less). The mean number of items recalled on the LMT was 37.0 in the tested group compared to 31.0 in the non-tested group, and the mean number of problems correctly completed in 20 minutes on the RPM was 35.2 versus 30.0, respectively. On the VFT, the tested group obtained a mean score of 39.5 compared to a mean score of 36.0 in the non-tested group (higher score indicates more words produced during a timed trial). Lastly, the mean DST score (indicating the number of correctly filled-in boxes in 90 seconds) in the tested group was 41.6 compared to a mean score of 35.5 among non-tested subjects.

5.4. NON-FATAL CARDIOVASCULAR DISEASES IN PARTICIPANTS IN THE SECOND ROUND OF COGNITIVE TESTING

5.4.1. Angina Pectoris

Angina pectoris was recorded at baseline if there was a) positive WHO questionnaire and positive ECG or b) positive WHO questionnaire and a recall of a doctor's diagnosis of angina. At follow-up, angina was noted if either of the above was present or a clinical diagnosis of angina was confirmed by either a GP or a hospital. Approximately 5.0 % (n=23) of subjects who underwent cognitive testing in 2002/3 met diagnostic criteria for angina at baseline in 1987/8. By February 2002 (the cut-off date for diagnosis of CVD in the current study), 25.0% (n=113) of subjects had accumulated a diagnosis of angina since baseline (see appendix F-1 for the number of subjects meeting individual confirmatory criteria).

A further comparison of subjects who were tested at the University clinic compared to those tested at home revealed no significant differences with respect to the numbers with angina. The results showed that 15.7% (n=34) of clinic subjects versus 20.0% (n=25) of those who were seen at home had history of angina (P=0.307).

5.4.2. Intermittent Claudication

Intermittent claudication was recorded if there was a positive response on the WHO questionnaire at baseline or during follow-up. Approximately 1.5% (n=7) of the cognitively tested subjects had reported intermittent claudication at baseline. By February 2002, the total number of subjects meeting criteria for claudication had increased to 13.7% (n=62) (see appendix F-2 for the number of subjects meeting individual confirmatory criteria).

The proportion ever having met criteria for intermittent claudication was compared in subjects cognitively tested at the clinic versus at home. The comparison revealed that 16.8% (n=37) of those tested at the clinic and 16.7% (n=20) of those tested at home had ever had intermittent claudication (P=0.971).

5.4.3. Myocardial Infarction

Myocardial infarction was noted if the following two out of three confirmatory criteria were met at baseline or during follow-up. At baseline the three criteria were: a) positive WHO questionnaire, b) ECG evidence of MI, and c) a recall of a doctor's diagnosis of the event. During follow-up, the three criteria were: a) elevated cardiac enzymes, b) ECG evidence of MI, and c) typical cardiac chest pain for 20 minutes or more. Among those who participated in the cognitive testing in 2002/3, 2.0% (n=9) met study criteria for diagnosis of MI at baseline. By the cut-off date for diagnosis of CVD, 11.7% (n=53) of subjects had either met baseline or follow-up criteria for MI (see appendix F-3 for the number of subjects meeting individual confirmatory criteria).

A further analysis involved comparing the number of subjects who had ever met study criteria for MI among those who were tested at the clinic versus at home. The results showed that 15.3% (n=33) to clinic subjects compared to 14.5% (n=17) of subjects tested at home had history of MI (P=0.855).

5.4.4. Stroke

Stroke was recorded at baseline or at a follow-up examination if there was a subject's recall of a doctor's diagnosis of the event, or on the presence of either of the following at any point during follow-up: a) history of onset of symptoms of less than 48 hours plus clinical confirmation of a focal or global disturbance of cerebral function lasting for more than 24 hours, or b) computerised scan (CT) showing evidence of cerebral infarction or haemorrhage. A history of stroke at baseline was confirmed in 1.3% (n=6) of subjects cognitively tested in 2002/3. By February 2002, 4.4% (n=20) of the sample had met either baseline or follow-up study criteria for stroke (see appendix F-4 for the number of subjects meeting individual confirmatory criteria).

An additional analysis focused on assessing the number of subjects meeting stroke criteria among those cognitively tested at the University clinic versus at home. The results revealed that, among those attending the clinic, only 1.6% (n=3) had ever had stroke compared to 12.3% (n=14) of subjects visited at home. The difference turned out to be statistically significant ($P<0.001$).

5.5. LEVELS OF CARDIOVASCULAR RISK FACTORS IN PARTICIPANTS IN THE SECOND ROUND OF COGNITIVE TESTING

Of the 452 subjects who were cognitively assessed in 2002/3, 32.7% were less than 75 years of age at the time of testing: 29.4% were aged between 75 and 79 years; 27.9% came from the 80-84 years age band; and 10.0% were 85 years or older. Approximately 50.0% of the sample were women (n=227). Baseline information on the highest level of education completed was available for 451 subjects (data missing for one subject). In total, 22.2% had completed University and

24.8% had finished post school training of some kind. Approximately 51.5% had completed secondary school and 1.3% had finished primary school. Most social classes were well represented in the sample. Based on the current, or the longest held, occupation when interviewed at baseline (or husband's occupation in the case of married women), 14.6% and 40.9% of subjects came from social classes I and II, respectively. Social class IIIN (non-manual) was represented by 21.0% of subjects, 15.7% came from social class IIIM (manual), and 7.5% of subjects belonged to social classes IV and V (these were combined due to small numbers).

Levels of several lifestyle variables were assessed at baseline according subjects' self-report. Physical activity levels were based on questions regarding current and past leisure activities. Complete data were available for all cognitively tested subjects and the following pattern was observed: 7.1% of subjects were physically inactive; 31.4% were engaged in light physical activity at most; 50.2% were engaged in moderate activity at most; and 11.3% were engaged in strenuous activity at most.

Assessment of alcohol intake referred to a typical week's alcohol consumption (units of alcohol consumed in a typical week). At baseline, 7.8% of subjects reported not having consumed any alcohol in the week prior to the baseline interview, 56.1% had consumed 1-2 units, 21.5% had had three units, and 14.6% had consumed four or more units of alcohol.

As above, self-reported data on smoking habits at baseline were available for a total of 446 cognitively tested subjects. Based on these, 14.9% and 40.9% of subjects were either current or former smokers, whereas 44.1% of subjects had never smoked.

5.6. UNIVARIATE DESCRIPTION OF COGNITIVE OUTCOMES

5.6.1. First Round of Cognitive Testing

As an early step in the statistical analysis of the cognitive test data, the central tendency and score distribution of each of the cognitive outcomes from 1998/9 was determined in the 452 subjects who were cognitively tested in 2002/3 (table 2). As defined, the mean general cognitive factor score for the sample was 0.00 (SD=1.00) and valid results were available for 411 subjects (41 missing). With regard to the individual cognitive tests, the mean LMT score (immediate and delayed recall combined) was 37.0 (SD=13.4) with valid data obtained from 447 subjects; the mean RPM score in the sample was 35.2 (SD=9.1) and complete data were available for 439 subjects; a mean score of 39.5 (SD=12.8) on the VFT (letters C, F, and L combined) was based on 447 subjects; and 417 subjects provided valid data on the DST (mean score=41.6; SD=10.8).

5.6.2. Second Round of Cognitive Testing

A similar data description to that above was carried out on the cognitive outcomes from the second round of cognitive testing. The mean general cognitive factor score of 0.00 (SD=1.00) was based on data from 424 subjects (data from 28 subjects were missing). Complete data on the LMT was obtained from 445 subjects (mean score of 38.5; SD=15.8) whereas 433 subjects provided valid data on the RPM (mean score of 32.5; SD=10.1). The mean total number of words produced on the VFT was 37.7 (SD=12.9) and valid data were available for 446 subjects. Lastly, 433 subjects had complete data on the DST (mean score of 36.2; SD=11.7).

5.7. BIVARIATE CORRELATIONS AMONGST COGNITIVE OUTCOMES

5.7.1. Outcomes from the Second Round of Cognitive Function Testing

Pearson's r product moment correlation coefficients were computed for all combinations of bivariate associations between the individual cognitive tests in 2002/3 in order to assess the direction and strength of their relationships. Overall, all the cognitive tests correlated at least moderately positively with each other. More specifically, the following was observed: The LMT correlated 0.46 with the RPM ($P<0.001$), 0.21 with the VFT ($P<0.001$), and 0.37 with the DST ($P<0.001$). The correlation coefficient for the relationship between the RPM and the VFT was 0.37

(P<0.001), and that between the RPM and the DST was 0.65 (P<0.001). The VFT and the DST also correlated positively (r=0.45; P<0.001).

5.7.2. Outcomes from First and Second Rounds of Cognitive Function Testing

Pearson's r correlation coefficients were also computed in order to assess the level of stability in individual differences in cognitive test performance over the four-year study interval. For each cognitive outcome, 1998/9 scores were correlated with the 2002/3 scores with missing values deleted on a listwise basis. The correlation coefficient for the 1998/9 and 2002/3 general cognitive factor scores measured 0.87 (P<0.001). Of the individual tests, the earlier and the latter LMT scores had a correlation coefficient of 0.71 (P<0.001), whereas that for the RPM scores was 0.77 (P<0.001). The earlier and the latter VFT and DST scores correlated still higher, 0.82 (P<0.001) and 0.85 (P<0.001), respectively.

5.8. LEVELS OF VASCULAR RISK FACTORS BY CARDIOVASCULAR STATUS

5.8.1. Sociodemographic Factors

Age

Mean age at the time of cognitive testing in 2002/3 was assessed in each of the CVD groups relative to that in non-diseased subjects (table 3). The mean age in subjects with evidence of any major CVD apart from stroke was 78.4 years (SD=4.9) compared to 77.1 years (SD=5.0) in subjects without CVD. The difference was statistically significant (P=0.011). When age was examined in the individual CVD categories, subjects with stroke had the highest mean age (79.5 years; SD=5.8) while the next highest was among subjects with intermittent claudication (78.7 years; SD=4.9). Subjects with angina had a mean age of 78.4 years (SD=5.0) and the mean age among those with MI was 78.3 years (SD=4.9). Only subjects with intermittent claudication had a statistically higher mean age relative to subjects without any CVD (P=0.033).

Sex

Relative to subjects without CVD, men were overrepresented (although non-significantly so) in all disease categories (table 3). As an example, men made up 55.0% of subjects with any CVD compared to 46.6% in the healthy group. Men represented 54.2% of subjects with angina, 49.1% of subjects with intermittent claudication, 62.0% of subjects with MI and 47.1% of subjects in the stroke group. Only the proportion of men with MI differed statistically from that in the group of healthy subjects (P=0.045).

Educational Level

Common to most of the vascular groups, diseased subjects were relatively less likely to have completed higher education (University or post school training) (table 3). For instance, among subjects with any CVD, the proportion having completed University was 16.8% compared to 25.5% in healthy subjects. The equivalent proportion among those with angina was 13.6%; 17.5% in the intermittent claudication group; 16.0% in those with MI; and 17.6% in stroke subjects. Likewise, relatively more diseased subjects had only completed primary or secondary education when interviewed at baseline. When evaluated statistically, the above trend turned out to be significant for subjects with any CVD (P=0.010), and those with intermittent claudication (P=0.022) and MI (P=0.016).

Occupational Social Class

Similar to that above, the association between social class and CVD was assessed by examining social class trends in relation to CVD status (table 3). In subjects having any CVD apart from stroke, a relatively lower proportion of subjects came from social classes I and II. For instance, 9.4% and 35.6% of subjects with any

CVD came from social classes I and II compared to 16.6% and 44.5% in the group of healthy subjects. These trends were statistically significant (P=0.001). Similar pattern was observed for the other vascular categories, yet only the trend among subjects with angina (P=0.002), intermittent claudication (P=0.041), and MI (P=0.024) was statistically significant.

5.8.2. Mood, Cognitive Status, and Prior Ability Level

Anxiety

Anxiety levels at the time of assessment of cognition in 2002/3 were evaluated using the HADS (table 4). Depending on the magnitude of the anxiety score for any given subject, individual case status was also estimated. Both median levels of anxiety and anxiety caseness were examined in relation to CVD status. The median anxiety score for subjects showing evidence of any CVD was 5.0 (IQR=3.0-8.0) relative to a score of 4.0 (IQR=2.0-6.0) in healthy subjects. The difference tested statistically significant (P<0.001). Higher median anxiety levels were also observed in subjects with angina (P=0.006) and MI (P=0.001). Moreover, elevated anxiety scores were found in subjects with intermittent claudication and stroke but the differences between these subjects and those without CVD failed to reach statistical significance.

In comparison to healthy subjects, relatively more of those with vascular disease had high enough scores on the anxiety sub-scale to suggest the presence of either possible or probable clinical anxiety. For instance, 18.1% of subjects with any CVD had scores indicating possible anxiety whereas 7.4% probably had anxiety around the time of testing (the equivalent proportions of subjects without CVD were 8.9% and 3.9%). The above trend tested statistically significant (P=0.002). Similar results were obtained for the individual CVD groups. Diseased subjects were in all instances statistically more likely to experience elevated anxiety levels relative to those without CVD.

Depression

In comparison to scores on the anxiety sub-scale (see above) HADS depression scores were generally lower in CVD subjects even though the same trends were more or less observed (table 4). As an example, the median depression score in subjects with any CVD was 4.0 (IQR=2.0-6.0) compared to a median score of 2.0 (IQR=1.0-4.0) in those without CVD ($P<0.001$). The median scores for the other CVD categories ranged from 3.5 in subjects with MI to 5.0 in those with intermittent claudication. Subjects with CVD had in all instances statistically elevated median depression scores relative to subjects without CVD. Leading on from these results, proportionately more diseased subjects had depression scores indicating possible or probable clinical depression.

Mini-Mental Status

Cognitive screening at the time of cognitive function testing in 2002/3 was performed using the MMSE. Due to the positive skewness of the MMSE scores, median levels were compared in diseased and healthy subjects using appropriate statistical methods (table 4). Overall, no statistically significant differences were observed between subjects with and without vascular disease despite comparatively lower median MMSE scores in all CVD groups. Due to the skewness in the data distribution, scores on the MMSE were generally very high and close to the upper limits of the scale (the median ranged from 28.0 to 28.5 across the CVD groups).

Peak Prior Cognitive Ability

Peak prior cognitive ability was estimated using the NART (table 4). A comparison of diseased and healthy subjects revealed marked differences in mean performance on the NART, which was based on the total number of correctly pronounced words. Specifically, subjects with CVD had significantly lower mean NART scores (the mean scores ranged from 29.8 in those with MI to 31.3 in the any

CVD group, all at least $P<0.01$) compared to those without any vascular disease (35.1). In contrast, subjects with stroke did not differ significantly from those without CVD.

5.8.3. Lifestyle Factors

Physical Activity

Physical activity levels at baseline were assessed in each CVD group relative to the group of healthy subjects (table 5). In general, relative to the comparison group, diseased subjects were less likely to be physically active at baseline (the opposite was true for the healthy group) even though most subjects (diseased and healthy) were engaged in some kind of exercise. No statistically significant trends were, however, observed for any of the exposure groups.

Alcohol Consumption

Median levels of self-reported intake of units alcohol consumed in a typical week were slightly elevated in subjects with CVD compared to healthy subjects (table 5). However, no statistically significant differences were observed. As an example, the median alcohol level in subjects with any CVD was 5.0 (IQR=1.0-15.0) compared to a median total units of alcohol of 4.0 (1.0-11.0) in the healthy group. Median levels in the other CVD groups ranged from 4.0 to 5.0. When divided into categories of total units alcohol consumed over the past week, no meaningful trends were observed.

Smoking

An analysis of baseline data on smoking revealed that, in general, subjects with CVD were more likely to smoke, and less likely to have never smoked, relative to those without CVD (table 5). Statistically elevated levels were, however, only noted in subjects with intermittent claudication (P=0.047). Approximately 27.8% of these subjects smoked at baseline, whereas only 11.7% of healthy subjects did; 42.6% of subjects with intermittent claudication had never smoked versus 47.6% of healthy subjects.

Reflecting the above pattern, median pack-years of smoking were normally higher in diseased subjects relative to those without CVD. As an example, the median pack-years in subjects with any CVD were statistically elevated (P=0.046), and of the individual disease groups, the highest median levels of pack-years were observed in subjects with MI (10.6; IQR=0.0-38.5; P=0.003) and stroke (36.0; IQR=0.0-40.0; P=0.005).

5.8.4. Physiological Variables

Body Mass Index

Calculation of the BMI at baseline was based on the measured height and weight of any given subject (table 6). The observed mean BMI score for subjects without CVD was 25.1 kg/m^2 (SD=3.3) whereas mean BMI values for diseased subjects ranged from 26.1 kg/m^2 (stroke) to 26.6 kg/m^2 (angina). In each of the CVD categories, subjects with stroke being the only exception, the mean BMI was statistically elevated relative to that of healthy subjects.

Glucose Tolerance

The majority of both diseased and healthy subjects had baseline blood glucose levels within normal limits (table 6). Overall, however, diseased subjects were more likely to have either impaired glucose tolerance, or clinical diabetes, in comparison to healthy subjects (the proportion with impaired glucose tolerance ranged from 8.9% to 15.5% across the CVD categories compared to 8.6% in subjects without CVD). Moreover, mean blood glucose levels (fasting blood glucose was assessed in non-diabetic subjects only) were elevated in most CVD groups (mean values ranged from 5.6-5.9 mmol/L) relative to healthy subjects (mean value equal to

5.6 mmol/L) even though none of the differences turned out to be statistically significant.

Blood Pressure

Mean baseline levels of both SBP and DBP were substantially higher in diseased subjects compared to those without CVD (table 6). Mean levels of SBP and DBP in healthy subjects measured 134.9 mmHg (SD=20.3) and 74.9 mmHg (SD=11.2), respectively. SBP levels in diseased subjects were on average 8.6 to 12.1 mmHg higher than in no CVD subjects (values ranged from 143.5 mmHg to 147.0 mmHg across CVD categories); mean DBP levels were on average 3.3 to 5.1 mmHg higher (values ranged from 78.2 mmHg to 80.0 mmHg). For the majority of CVD groups, the elevated blood pressure levels differed statistically from that in healthy subjects.

Blood Lipids

Mean total cholesterol levels at baseline were elevated across most disease groups and ranged from 6.9 to 7.4 mmol/L (table 6). In comparison, healthy subjects had a mean level of 7.0 mmol/L. Similarly, mean LDL levels were generally higher in diseased subjects (levels ranged from 5.2 to 5.7 mmol/L) compared to those without CVD (5.2 mmol/L). In contrast, mean levels of HDL were statistically significantly reduced in most groups of subjects with CVD (levels ranged from 1.3 to 1.6 mmol/L compared to a mean value of 1.5 mmol/L in subjects without CVD).

In a similar manner, both median levels of lipoprotein (a) and mean triglyceride levels were comparatively higher across most of the CVD categories. Overall, however, no statistically significant differences in baseline levels of these factors were observed between diseased and healthy subjects.

Homocysteine

Mean plasma levels of homocysteine (measured at 5-year follow-up) were elevated in subjects with any CVD, and in those with intermittent claudication and MI, relative to healthy subjects (table 6). The observed mean levels were 11.9 (P=0.077), 12.8 (P=0.029), and 13.0 μmol/L (P=0.020) versus 11.2 μmol/L in the group of subjects without CVD, respectively. Comparatively lower mean levels of homocysteine were observed in both subjects with angina and stroke but not to a statistically significant degree.

5.8.5. Levels of Haemostatic, Inflammatory and Rheological Factors

Fibrinogen

Mean plasma fibrinogen levels were elevated in all groups of diseased subjects relative to healthy subjects (2.6 to 2.8 g/L versus 2.5 g/L) (table 7). Statistically higher levels were observed in subjects with any CVD (P=0.003) and in those with intermittent claudication (P<0.001).

D-Dimer

Mean levels of the fibrinogen degradation product D-dimer ranged from 82.9 to 95.5 μg/mL in subjects with CVD compared to 78.7 μg/mL in subjects without CVD (table 7). Only in subjects with any CVD (P=0.015) and those with intermittent claudication (P=0.022) were the mean levels statistically elevated.

C-Reactive Protein

Median baseline levels of CRP were statistically significantly raised in all CVD categories relative to healthy subjects (median level of 1.1 mg/L) (table 7). Median levels ranged from 1.5 to 2.5 mg/L in those with evidence of CVD and the highest comparative levels were observed in subjects with intermittent claudication (P=0.002) and stroke (P=0.018).

Interleukin-6

In comparison to subjects without CVD, baseline median levels of IL-6 were elevated across all CVD categories (table 7). Median levels ranged from 1.8 to 3.4 pg/mL in subjects with CVD (statistically raised levels were observed in subjects with any CVD and in those with intermittent claudication and MI) versus a median level of 1.6 pg/mL in the comparison group.

Cellular Adhesion Molecules

Baseline serum levels of three types of cellular adhesion molecules were determined and compared in diseased and healthy subjects: ICAM-1, VCAM-1, and E-selectin (table 7). Overall, mean levels of these factors were elevated across all CVD groups. Mean levels of ICAM-1 were, however, only statistically significantly raised in subjects with any CVD (P=0.029) and in those with intermittent claudication (P=0.011); mean E-selectin levels were only statistically higher in subjects with any CVD (P=0.032). No statistically significant associations between CVD status and VCAM-1 levels were observed.

Blood Viscosity

Whole blood viscosity levels varied between healthy and diseased subjects (table 7). Mean levels were statistically significantly elevated across all CVD groups relative to that in subjects without CVD (values ranged from 3.6 to 3.7 mPa/sec versus 3.4 mPa/sec in the comparison group). Similar results were obtained for plasma viscosity despite fewer of the differences between diseased and healthy reaching statistical significance.

Haematocrit

Mean levels of percentage haematocrit were found to be comparatively higher across all CVD groups (table 7). Mean values ranged from 45.8% in subjects with intermittent claudication and MI to as high as 46.5% in subjects with stroke. In comparison, the mean haematocrit level in healthy subjects was 45.1%. Statistically elevated levels were only observed in subjects with any CVD and in those with angina.

5.9. FOUR-YEAR CHANGE IN MEAN COGNITIVE TEST SCORES BY CARDIOVASCULAR STATUS: UNADJUSTED BIVARIATE ANALYSES

5.9.1. Logical Memory

Data on LMT performance in 1998/9 were available for 279 healthy and 148 diseased subjects (any CVD) (figure 2). Whereas healthy subjects had a mean score of 37.0 (SD=13.0), the diseased group obtained a mean of 37.5 (SD=13.9). Over the four-year interval, mean scores improved in the healthy group (mean score=40.0; SD=15.1; N=277) but declined slightly in subjects with any vascular disease (mean score=37.3; SD=16.2; N=148). In contrast, subjects with angina had a mean score of 37.9 (SD=13.4; N=59) in 1998/9 but a higher mean score of 39.0 (SD=16.8; N=58) in 2002/3. Whereas subjects with intermittent claudication, MI, and stroke all showed a four-year decline in mean LMT scores, the decrease was relatively greatest in the stroke group. Thus, in 1998/9, the following results were obtained for the three groups: intermittent claudication (mean score=36.7; SD=14.8; N=57), MI (mean score=35.5; SD=13.4; N=49), stroke (mean score=33.5; SD=16.2; N=17). The 2002/3 results revealed the following: intermittent claudication (mean score=35.2; SD=15.5; N=57), MI (mean score=35.2; SD=15.9; N=50), stroke (mean score=29.5; SD=18.9; N=17).

5.9.2. Raven's Standard Progressive Matrices

In contrast to that above, a more distinctive pattern of four-year decline in RPM performance was observed across all groups of healthy and diseased subjects (figure 3). In 1998/9, subjects without CVD had a mean RPM score of 36.1 (SD=9.2; N=276) whereas subjects with any CVD had a mean of 33.7 (SD=8.6; N=144). In 2002/3, a lower mean RPM score was observed in both groups: 274 healthy subjects obtained a mean of 33.8 (SD=10.0) while 141 subjects with any CVD had a mean score of 30.5 (SD=9.8). In subjects with angina, the mean RPM score in 1998/9 was 33.9 (SD=9.6; N=55) and 32.3 (SD=10.4; N=53) in 2002/3. The mean score in subjects with intermittent claudication declined by almost four points over the four years (the mean score in 1998/9 was 32.9; SD=8.1; N=57 and in 2002/3 it was 29.0; SD=9.1; N=55). In the group of subjects with MI, the mean score decline from 33.8 (SD=8.2; N=49) in 1998/9 to 28.8 (SD=9.3; N=50) in 2002/3. A slightly less decline was observed among those with stroke; the mean decreased from 32.2 (SD=11.9; N=16) in 1998/9 to 28.6 (SD=12.0; N=15) in 2002/3.

5.9.3. Verbal Fluency

An overall decline in mean VFT scores over the four years was observed in both healthy subjects and across all CVD groups (figure 4). Subjects without CVD had a mean score of 40.9 (SD=12.5; N=282) in 1998/9, whereas a mean score of 37.7 (SD=12.7; N=146) was reported in subjects with any CVD. In 2002/3, the mean score in the former group had decreased to 39.2 (SD=12.9; N=280), while that in the latter was 36.3 (SD=12.3; N=146). In subjects with angina, a mean score of 38.9 (SD=11.6; N=58) was observed in 1998/9 whereas in 2002/3 the mean score was 37.1 (SD=11.1; N=57). In subjects with intermittent claudication, MI, and stroke, the following was noted: in 1998/9, subjects with intermittent claudication had a mean score of 34.6 (SD=12.1; N=56), those with MI had a mean of 36.8 (SD=14.2; N=49), and the stroke group had a mean of 32.1 (SD=14.1; N=16); in 2002/3, the mean score in those with intermittent claudication had decreased to 34.3 (SD=11.5; N=56), whereas that in subjects with MI was 36.1 (SD=14.2; N=50), and 29.6 among subjects with stroke (SD=13.3; N=17).

5.9.4. Digit Symbol-Coding

In general, mean DST scores declined over time in both subjects with and without CVD (figure 5). In healthy subjects, the mean score in 1998/9 was 43.5 (SD=10.8) and valid data were obtained for 267 subjects. Equivalently, the mean score in diseased subjects (any CVD) was 38.7 (SD=9.9; N=135). In 2002/3, the mean scores had decreased for both groups: the mean score for subjects without CVD was 38.3 (SD=11.6) whereas that for subjects with any CVD was 33.1 (SD=11.0; N=143), or almost five points lower. In subjects with angina, the mean DST score had decreased by more than five points over the four-year interval (the mean score in 1998/9 was 40.2; SD=10.9; N=50, while in 2002/3 it was 34.4; SD=12.9; N=54). The four-year decline in mean scores among subjects with intermittent claudication was slightly lower than that in angina subjects: the mean score in 1998/9 was 36.0 (SD=9.4; N=54), whereas the mean score in 2002/3 was 31.6 (SD=8.9; N=56). A larger decline of almost six points was observed in subjects with MI who had a mean score of 37.8 (SD=8.9; N=47) in 1998/9 and a mean of 32.0 (SD=10.2; N=50) in 2002/3. In stroke patients, however, a decline of almost seven points was observed over the four-year period (the stroke group had a mean score of 35.2; SD=9.9; N=12 in 1998/9 and of 29.4; SD=10.8; N=15 in 2002/3).

5.10. COGNITIVE PERFORMANCE IN 2002/3 BY CARDIOVASCULAR STATUS: MULTIVARIATE ANALYSIS

5.10.1. General Factor Scores

Baseline Performance-Adjusted Analysis

Adjusting for baseline differences in general cognition (in addition to age and sex), attenuated the mean differences in general factor scores at follow-up between subjects with any CVD and those without vascular disease so they no longer remained statistically significant (tables 8-12). Similar patterns were noted for the individual CVD categories as well. However, angina was not significantly associated with general cognition either before or after control for baseline factor scores. The mean differences between subjects with intermittent claudication and those without CVD decreased (the change in significance level was from P=0.001 to P=0.028) after adjustment for baseline general factor levels; for the MI group, the difference was attenuated beyond statistical significance. Subjects with stroke had a borderline statistically (P=0.047) lower age, sex, and 1998/9 score adjusted mean general cognitive factor score relative to healthy subjects.

Results from the regression analysis of the relationship between intermittent claudication and general cognitive factor scores are presented in table 13. In addition to age, sex, and earlier general cognitive factor scores, only BMI turned out to be independently related to the dependent variable when included with these core factors (factors that were examined but did not contribute independently to the model included: education, depression, SBP, DBP, HDL, LDL, homocysteine, fibrinogen, D-dimer, CRP, IL-6, ICAM-1, blood and plasma viscosity). Essentially no change occurred in the intermittent claudication - general cognitive factor association (B decreased from -0.15 to -0.14) when BMI was added (model 3). In the final model, which accounted for approximately 79.7% (adjusted R^2) of the variance in the outcome variable (F(5,300)=240.80; P<0.001), the following terms made an independent contribution: intermittent claudication (B=-0.14/standardized beta=-0.05; t(300)=-2.06; P=0.040), which explained about 0.29% of the variance in general cognitive factor, earlier general cognitive factor scores (B=0.84/standardized beta=0.86; t(300)=31.13; P<0.001), and BMI (B=-0.01/standardized beta=-0.05; t(300)=-2.03; P=0.043).

Similar to above, the association between stroke and the general cognitive factor were further examined using multiple regression (table 14). The analysis showed that none of the CVD risk factors investigated for inclusion in the analysis (place of cognitive testing, depression, pack-years of smoking, SBP, CRP, and blood viscosity) contributed independently when added to the model containing the core adjustment variables (age, sex, and 1998/9 general cognitive factor scores). As a result, the final model contained these core variables in addition to the stroke term. Only stroke (B=-0.29/ standardized beta=-0.06; t(261)=-1.99; P=0.047), which explained about 0.32% in the variance of the outcome variable, and earlier general cognitive factor scores (B=0.84/standardized beta=0.86; t(261)=28.41; P<0.001) contributed independently in the final model (adjusted R^2= 78.8%; F(4,261)=247.23; P<0.001).

Peak Prior Cognitive Ability-Adjusted Analysis

Initially, age and sex-adjusted mean general cognitive factor scores were compared in healthy and diseased subjects, examining first subjects with any CVD (tables 15-19). A statistically significant difference in age and sex adjusted mean scores was observed between these subjects and those without CVD (P=0.002). Further adjustment for peak prior ability as estimated by performance on the NART attenuated the difference so it no longer remained significant. No statistically significant differences were detected in mean general cognitive factor scores between subjects with angina and those without CVD, either before or after adjusting for peak prior ability level. A mean difference in age and sex-adjusted means between subjects with intermittent claudication and those without CVD decreased when adjustment for prior ability was made so it no longer remained significant. An even greater attenuation in mean general cognitive factor scores was observed when peak prior ability was adjusted for in a comparison of subjects with MI and those without CVD. Finally, stroke subjects had statistically lower age and sex-adjusted mean general cognitive factor score than subjects without CVD; further adjustment for peak prior ability led to a slight increase in the observed difference which also became more statistically significant (change in P from 0.009 to <0.001).

Further analysis of general cognitive factor scores in subjects with stroke was carried out using multiple linear regression (table 20). The following were considered for inclusion in the regression analysis, in addition to age, sex, and prior ability: place of cognitive testing, depression, smoking, systolic blood pressure, C-reactive protein, and blood viscosity. Significantly elevated levels of these factors were found in stroke subjects compared to subjects without CVD. Only blood viscosity was independently associated with the general cognitive factor when added to a regression model controlling for age, sex, and prior ability. The incorporation of blood viscosity led to a slight attenuation (the unstandardised B coefficient decreased from -0.70 to -0.59) in the association of stroke with the general cognitive factor (model 3). In this final model, stroke remained independently associated with the outcome variable (B=-0.59/standardized beta=-0.11; t(232)=-2.33; P=0.021), accounting for 1.25% of the variance, along with age (B=-0.07/standardized beta=-0.36; t(232)=-7.60; P<0.001), prior ability (B=0.06/standardized beta=0.55; t(232)=11.44; P<0.001), and blood viscosity (B=-0.22/standardized beta=-0.11; t(232)=-2.29; P=0.023). Taken together, approximately 47% of the variance (based on the adjusted R^2) in the general cognitive factor was explained by the final regression model (F(5,232)=43.57; P<0.001).

5.10.2. Logical Memory

Baseline Performance-Adjusted Analysis

A comparison of age and sex adjusted mean LMT scores across CVD categories (tables 8-12) revealed that only in subjects with stroke was the mean score statistically lower than in healthy subjects. Subjects with MI had, on average, a lower mean LMT score but the difference from that of healthy subjects failed to reach statistical significance. When further adjustment involving performance on the LMT in 1998/9 was performed, the mean differences between healthy and diseased subjects became more exacerbated. For example, a statistically lower mean score was observed for the group of subjects with any CVD. Moreover, subjects with intermittent claudication, MI, and stroke all performed significantly worse than those without CVD.

Further analysis initially focused on the association of any CVD with 2002/3 LMT scores (table 21). Of the individual CVD risk factors that were considered for inclusion in the model (putative confounding factors that failed to contribute independently in the model included social class, anxiety, depression, pack-years of smoking, BMI, SBP, DBP, HDL, LDL, D-dimer, CRP, IL-6, ICAM-1, E-Selectin, haematocrit, and blood and plasma viscosity) containing the core adjustment variables (age, sex, and 1998/9 LMT scores), education was first entered alone (model 3), and then fibrinogen was entered separately (model 4). The final model (model 5) included both these factors in addition to age, sex, and 1998/9 LMT scores. Addition of education led to attenuation in the association of any CVD with LMT scores (increase in B from -2.67 to -2.19), whereas incorporation of fibrinogen strengthened the association (B decreased from -2.67 to -3.04). A slight reduction in the main association occurred when both factors were included (B=-2.56 in model 5). As a result, the final model included the following independent factors: any CVD (B=-2.56/standardized beta=-0.08; t(402)=-2.22; P=0.027), age (B=-0.23/ standardized beta=-0.07; t(402)=-2.03; P=0.043), 1998/9 LMT scores (B=0.77/ standardized beta=0.67; t(402)=18.46; P<0.001), education (B=-1.95/standardized beta=-0.11; t(402)=-2.88; P=0.004), and fibrinogen (B=2.25/standardized beta=0.09; t(402)=2.47; P=0.014). Around 0.62% of the variance in 2002/3 LMT scores was explained by the any CVD term whereas the proportion accounted for by the model as a whole was approximately 51% (adjusted R^2=51.3%; F(6,402)=72.56; P<0.001).

Identical approaches were used in the regression analysis of the relationship of the other CVD categories with 2002/3 LMT scores. For example, a series of regression models were created for the purpose of investigating the relation of intermittent claudication with LMT scores (table 22). In addition to the core confounders, the following were included in the models (factors that were examined but did not contribute independently to the model included: depression, SBP, HDL, LDL, homocysteine, D-dimer, CRP, IL-6, ICAM-1, blood and plasma viscosity), first each on its own in addition to the basic confounders, and then cumulatively: education, diastolic blood pressure, and fibrinogen. Inclusion of education (model 3) attenuated the intermittent claudication-LMT association somewhat (change in B from -4.01 to -3.29), as did adjustment for diastolic blood pressure (B increased from -4.01 to -3.68) (model 4). Adjusting for fibrinogen strengthened the intermittent claudication-LMT association (B decreased from -4.01 to -4.78) (model 5). Cumulatively, adjusting for education and diastolic blood pressure led to an even further attenuation in the intermittent claudication-LMT association (B increased from -4.01 to -2.92), whereas adding fibrinogen to this model increased the strength of the association so that it became statistically significant. Therefore, in the final model (model 7), the following made an independent contribution to the variance in 2002/3 LMT scores: intermittent claudication (B=-3.72/standardized beta=-0.09; t(315)=-2.35; P=0.020), 1998/9 LMT scores (B=0.74/standardized beta=0.66; t(315)=16.34; P<0.001), education (B=-2.56/standardized beta=-0.143; t(315)=-3.53; P<0.001), diastolic blood pressure (B=-0.10/standardized beta=-0.08; t(315)=-2.00; P=0.047), and fibrinogen (B=2.71/standardized beta=0.11; t(315)=2.62; P=0.009). The intermittent claudication term was found to contribute approximately 0.88% to the variance in the dependent variable whereas just over 50% of the variance was explained by the model as a whole (adjusted R^2=52.3%; F(7,315)=51.42; P<0.001).

In the analysis of the association of MI with LMT scores in 2002/3, education (other putative confounding factors that failed to contribute independently in the model included social class, anxiety, depression, pack-years of smoking, BMI, SBP, DBP, HDL, homocysteine, CRP, IL-6, and blood viscosity) was added to the model containing age, sex, and 1998/9 LMT scores (table 23). This attenuated the MI-LMT association so that it no longer remained statistically significant (B increased from -3.36 to -2.80). This final model (model 3) accounted for almost 50% of the total variance in 2002/3 LMT scores (adjusted R^2=49.9%; F(5,316)=64.90; P<0.001). The following were independently related to the outcome variable: 1998/9 LMT scores (B=0.76/standardized beta=0.66; t(316)=15.99; P<0.001) and education (B=-1.71/ standardized beta=-0.10; t(316)=-2.29; P=0.023).

An even simpler final model was obtained as a result of a regression analysis of the stroke-LMT association which consisted solely of the core adjustment variables (table 24). None of the CVD risk factors evaluated contributed independently when added to the basic model (these included place of cognitive testing, depression, pack-years of smoking, SBP, CRP, and blood viscosity). In this final model, stroke was independently related to 2002/3 LMT scores (B=-7.17/standardized beta=-0.11; t(286)=-2.61; P=0.010) and accounted for 1.21% of the total variance. Earlier LMT scores also made an independent contribution (B=0.77/standardized beta=0.67; t(286)=15.46; P<0.001), whereas the model as a whole explained around 49% of the total variance (adjusted R^2=49.1%; F(4,286)=70.98; P<0.001).

Peak Prior Cognitive Ability-Adjusted Analysis

With the exception of stroke, no statistical differences were observed in age and sex adjusted mean LMT scores between healthy and diseased subjects (tables 15-19). Non-significant differences were further attenuated when peak prior ability was adjusted for. Stroke subjects had an age and sex adjusted mean score which, on average, was 8.9 points lower than in healthy subjects. When peak prior ability was adjusted for, the mean difference still remained significant (P=0.028).

As shown in table 25, a regression analysis of the relationship of stroke with LMT scores which led to the inclusion of C-reactive protein (other factors considered but did not contribute independently to the model included place of cognitive testing, depression, pack-years of smoking, SBP, and blood viscosity) resulted in a slightly stronger association which, however, remained non-significant (change in B from -3.25 (model 2) to -5.78 (model 3)). In the final model, which accounted for approximately 25% of the variance in 2002/3 LMT scores (adjusted R^2=24.6%; F(5,199)=14.28; P<0.001), the following factors were independently related to the outcome variable: age (B=-0.91/ standardized beta=-0.30; t(199)=-4.63; P<0.001), peak prior ability (B=0.77/ standardized beta=0.42; t(199)=12.94; P<0.001), and C-reactive protein (B=1.36/ standardized beta=0.24; t(199)=2.94; P<0.001).

5.10.3. Raven's Standard Progressive Matrices

Baseline Performance-Adjusted Analysis

Adjusting for 1998/9 RPM scores resulted in a substantial reduction in the differences in mean RPM scores in 2002/3 between diseased and healthy subjects (tables 8-12). Whereas differences in mean scores were no longer observed between healthy subjects and those with any CVD, angina, or stroke, subjects with MI had statistically lower scores and those with intermittent claudication had a lower score of borderline significance.

Table 26 presents the results from the regression analysis of the association of intermittent claudication with 2002/3 RPM scores. Separate models were computed for each CVD risk factor (along with the core adjustment variables) in order to demonstrate both the effects each had on the intermittent claudication-RPM association, as well as their cumulative impact. The factors that were included (factors that were examined but did not contribute independently to the model included: depression, SBP, DBP, HDL, LDL, homocysteine, D-dimer, CRP, IL-6 and plasma viscosity) in the analysis were: education, fibrinogen, ICAM-1, and blood viscosity. The analysis revealed that separately, each CVD risk factor led to a modest attenuation in the intermittent claudication-RPM association: addition of education increased B from -1.39 to -1.06 (model 3), addition of fibrinogen increased B from -1.39 to -1.28 (model 4), inclusion of ICAM-1 resulted in an increase in B from -1.39 to -1.23 (model 5), and adding blood viscosity increased B from -1.39 to -1.24 (model 5). In none of these analyses did the intermittent claudication-RPM association become statistically significant. When added cumulatively, each factor resulted in an even greater attenuation in the strength of the relationship of intermittent claudication with RPM scores. An increase in B from -1.39 to -0.98 was observed in model 7 (with education and fibrinogen in addition to core adjustment variables), a change from -1.39 to -0.89 in B resulted when ICAM-1 was added (model 8), and lastly in model 9, blood viscosity increased the value of B even further. In the final model, which was found to explain approximately 60% of the total variance (adjusted R^2=60.2%; F(8,208)=41.78; P<0.001), only age (B=-0.27/ standardized beta=-0.13; t(208)=-2.90; P=0.004) and 1998/9 RPM scores (B=0.76/ standardized beta=0.66; t(208)=13.55; P<0.001) made an independent contribution.

The final MI model included only the core adjustment variables since none of the CVD risk factors examined (social class, anxiety, depression, pack-years of smoking, BMI, SBP, DBP, HDL, homocysteine, CRP, IL-6, and blood viscosity) contributed independently when added to the model (table 27). In this model (model 2), MI was independently related to the dependent variable and contributed 0.90% to the total variance (B=-2.65/standardized beta=-0.10; t(315)=-2.69; P=0.007) whereas the model as a whole explained approximately 61% (adjusted R^2=61.1%; F(4,315)=126.04; P<0.001). Age (B=-0.22/standardized beta=-0.11; t(315)=-3.03; P=0.003) and 1998/9 RPM scores (B=0.81/standardized beta=0.72; t(315)=19.72; P<0.001) also contributed independently in the final model.

Peak Prior Cognitive Ability-Adjusted Analysis

An analysis of age and sex adjusted mean RPM scores revealed statistically lower scores in subjects with any CVD, intermittent claudication, and in those with MI, relative to subjects without CVD (tables 15-19). Further adjustment for peak prior ability resulted in a substantial attenuation in these associations. As a result, statistically significant differences were no longer observed. As a consequence, no further analysis was carried out on the cross-sectional association of CVD status with 2002/3 RPM scores.

5.10.4. Verbal Fluency

Baseline Performance-Adjusted Analysis

Adjustment for performance on the VFT in 1998/9 substantially reduced the magnitude of the age and sex adjusted mean VFT differences observed between diseased and healthy subjects (tables 8-12). As an example, the mean difference between healthy and subjects with intermittent claudication was reduced so it became non-significant. A similar attenuation was seen for the mean difference between subjects with stroke and those without CVD. Because CVD was no longer associated with cognition in any of the comparisons of mean scores, no further analyses were carried out on the data.

Peak Prior Cognitive Ability-Adjusted Analysis

Statistically lower age and sex adjusted mean VFT scores were observed in subjects with intermittent claudication, and in those with stroke, compared to healthy subjects (tables 15-19). Inclusion of peak prior ability attenuated these differences, but whereas the mean score for subjects with stroke remained statistically lower relative to that for healthy subjects, the difference between healthy and subjects with intermittent claudication became non-significant.

The association between stroke and 2002/3 VFT scores was further examined using multiple regression (table 28). A final model explaining close to 26% of the total variance in 2002/3 VFT scores (adjusted R^2=25.6%; F(4,288)=26.17; P<0.001) included only the stroke term in addition to the core adjustment variables (place of cognitive testing, depression, pack-years of smoking, SBP, CRP, and blood viscosity were examined as putative confounders but failed to contribute independently to the model). The contribution of the stroke term to the total variance in the outcome variable was 1.80% (B=-7.61/standardized beta=-0.13; t(288)=-2.62; P=0.009). Age (B=-0.32/ standardized beta=-0.12; t(288)=-2.44; P=0.015) and NART (B=0.71/standardized beta=0.48; t(288)=9.46; P<0.001) also made an independent contribution in the final model.

5.10.5. Digit Symbol-Coding

Baseline Performance-Adjusted Analysis

Adjusting for 1998/9 DST performance led to substantial attenuation of all age and sex adjusted differences in the follow-up scores so that they no longer remained significant (tables 8-12). It was therefore decided, that no further analyses would be performed on the above data.

Peak Prior Cognitive Ability-Adjusted Analysis

Relative to subjects without CVD, the mean age and sex adjusted 2002/3 DST scores were significantly lower in subjects with any CVD, and among those with intermittent claudication, MI, and stroke (tables 15-19). A further adjustment for peak prior ability reduced these differences so that, although the association of any CVD, intermittent claudication, and stroke with DST scores remained statistically significant, having MI was no longer associated with lower mean DST scores.

Results based on a further examination of the relationship between any CVD and DST are presented in table 29. The CVD risk factors included in the analysis were (other putative confounding factors that failed to contribute independently in the model included social class, BMI, HDL, LDL, D-dimer, CRP, ICAM-1, E-Selectin, and plasma viscosity): anxiety, depression, smoking, systolic and diastolic blood pressure, interleukin-6, haematocrit, and blood viscosity. Adjusting for each of these factors at a time led to a reduction in the magnitude of the any CVD-DST association (models 3 through 10). Whereas inclusion of interleukin-6 resulted in the largest relative reduction in the any CVD-DST relationship (B increased from -1.82 to -1.16) most of the other factors led to attenuation of similar size. In none of these models did vascular disease exert independent influence on DST scores. When the above factors were added in a cumulative fashion (models 11 through 17), there was a progressive decrease in the strength of the any CVD-DST relationship which at no point was found statistically significant. In the final model (model 17), which accounted for approximately 38% of the variance in DST scores (adjusted R^2=38.3%; $F(12,244)=14.23$; $P<0.001$), the following factors were found to contribute independently to the outcome variable: age (B=-0.88/standardized beta=-0.37; $t(244)=-6.37$; $P<0.001$), peak prior ability (B=0.41/standardized beta=0.31; $t(244)=6.01$; $P<0.001$), smoking (B=-0.55/standardized beta=-0.12; $t(244)=-2.30$; $P=0.022$), and interleukin-6 (B=-2.94/standardized beta=-0.15; $t(244)=-2.61$; $P=0.010$).

A regression analysis of the association of intermittent claudication with DST scores resulted in the addition of interleukin-6 to the model (other factors that were examined but did not contribute independently to the model included: education, depression, SBP, DBP, HDL, LDL, homocysteine, fibrinogen, D-dimer, CRP, ICAM-1, blood and plasma viscosity) consisting of the core adjustment variables (table 30). The result was a slight reduction in the strength of the intermittent claudication-DST relationship which remained non-significant (B increased from -3.23 to -2.25). However, age (B=-0.91/standardized beta=-0.39; $t(218)=-6.85$; $P<0.001$), peak prior ability (B=0.45/standardized beta=0.34; $t(218)=6.12$; $P<0.001$), and IL-6 (B=-2.74/standardized beta=-0.14; $t(218)=-2.29$; $P=0.023$) all contributed independently in the final model which accounted for close to 33% of the total variance in DST (adjusted R^2=32.7%; $F(5,218)=22.65$; $P<0.001$).

Finally, the relationship of stroke with DST scores is presented in a series of regression models in table 31. Levels of smoking and blood viscosity were found to be relatively elevated in stroke subjects and were considered for inclusion in the analysis (other factors considered included place of cognitive testing, depression, SBP, and CRP). Addition of smoking to model 2 (adjusting for age, sex, and peak prior ability) resulted in a slight attenuation in the stroke-DST association which remained non-significant (B increased from -6.61 to -5.26), and incorporation of blood viscosity reduced the strength of the association somewhat more (an increase in B from -6.61 to -4.88). In the final model, which in addition to the core variables also included terms for both smoking (B=-0.59/standardized beta=-0.12; t(231)=-2.26; P=0.025) and blood viscosity (B=-2.97/standardized beta=-0.13; t(231)=-2.31; P=0.022), stroke did not make an independent contribution to DST performance. Age (B=-0.99/standardized beta=-0.42; t(231)=-7.93; P<0.001) and peak prior ability (B=0.45/standardized beta=0.34; t(231)=6.45; P<0.001) were also independently related to DST scores. As a whole, the final model accounted for around 35% of the variance in DST scores (adjusted R^2=34.7%; F(6,231)=21.98; P<0.001).

5.11. GENERAL FACTOR-ADJUSTED RESIDUALS OF INDIVIDUAL COGNITIVE TESTS IN 2002/3 BY CARDIOVASCULAR STATUS: MULTIVARIATE ANALYSIS

5.11.1. Logical Memory

Baseline Performance-Adjusted Analysis

Rather than using the raw LMT scores as a dependent variable, the outcome variable in the current analysis comprised the general factor-adjusted standardised residuals of the LMT, which were computed by regressing the LMT on the general factor. As shown in table 32, after adjustment for age and sex, any vascular disease was not associated with the outcome (model 1). Further control for LMT performance in 1998/9 and other potential confounders attenuated the relationship between any CVD and the LMT residuals even further. However, in none of the models did the vascular term exert independent effects on the outcome. In the final model, age (standardised beta=0.03; t(384)=3.15; P=0.002), LMT performance in 1998/9 (standardised beta=0.04; t(384)=11.9; P<0.001), and baseline fibrinogen levels (standardised beta=0.23; t(384)=3.25; P=0.001) were significantly associated with the LMT residual scores. The model as a whole explained approximately 28% of the total variance in the dependent variable (R^2=28.2%; F(6,384)=26.48; P<0.001).

Similar to above, the relation of intermittent claudication with LMT residuals was examined and the results are presented in table 33. In the age and sex adjusted model (model 1), intermittent claudication did not significantly predict the LMT residual scores. Further adjustment for 1998/9 LMT performance and other potential confounding factors led to further attenuation in the association of intermittent claudication with the outcome variable. In the final model, age (standardised beta=0.03; t(303)=2.59; P=0.010), prior LMT scores (standardised beta=0.04; t(303)=9.43; P<0.001), and fibrinogen levels (standardised beta=0.24; t(303)=2.77; P=0.006) were independently associated with the dependent variable. The final model, however, explained close to 23% of the total variance in the outcome variable (R^2=22.9%; F(7,303)=14.17; P<0.001).

Lastly, the LMT residual scores were studied in relation to both MI and stroke. Having MI was not related to the outcome variable when adjusted for age, sex, 1998/9 LMT performance, and level of education (see table 34). In the final model, which accounted for about 22% of the total variance in LMT residual scores (R^2=21.8%; F(5,308)=18.41; P<0.001), only age (standardised beta=0.03; t(308)=3.12; P=0.002) and 1998/9 performance (standardised beta=0.04; t(308)=9.39; P<0.001) remained independent predictors of LMT residual scores. Identically, stroke neither significantly predicted LMT residual scores in models first adjusted for age and sex, and then additionally for prior performance (see table 35). Only age (standardised beta=0.02; t(275)=2.28; P=0.024) and 1998/9 LMT performance (standardised beta=0.03; t(275)=8.20; P<0.001) significantly predicted the outcome in a model which accounted for approximately 18% of the total variance (R^2=18.5%; F(4,275)=16.83; P<0.001).

Peak Prior Cognitive Ability-Adjusted Analysis

As shown in table 36, stroke was not associated with the outcome in any of the models (models 1 to 3). Further adjustment for peak prior ability did not change the association of stroke with the LMT residual scores, but further addition of CRP (model 3) led to a greater attenuation in the stroke-LMT association. In the final model, which accounted for less than 4.0% of the total variance in the dependent variable (R^2=3.9%; F(5,193)=2.61; P=0.026), only CRP remained an independent predictor of the outcome (standardised beta=0.23; t(193)=3.25; P=0.001).

5.11.2. Raven's Standard Progressive Matrices

Baseline Performance-Adjusted Analysis

Whereas no further peak prior cognitive ability-adjusted analysis of the relation of CVD with residuals of the RPM test was carried out, the association of both intermittent claudication and MI with the RPM residual scores was performed, controlling for RPM performance in 1998/9. The analysis of the intermittent claudication-RPM residual association which is presented in table 37 failed to establish a relationship between the two. More specifically, in none of the models examined was having intermittent claudication related to the outcome variable. Further addition of potential confounding factors to age, sex, and 1998/9 RPM performance-adjusted models changed the intermittent claudication-RPM residual score association only negligibly. The final model (model 9) was found highly significant (R^2=13.4%; F(8,202)=5.07; P<0.001) and the following contributed independently to the outcome: sex (standardised beta=-0.43; t(202)=-3.09; P=0.002) and 1998/9 RPM performance scores (standardised beta=0.04; t(202)=4.57; P<0.001). Similarly, MI was not related to the RPM residual scores in two models, one adjusting for age and sex, and another further controlling for RPM performance in 1998/9 (see table 38). Again, however, only sex (standardised beta=-0.32; t(310)=-3.13; P=0.002) and 1998/9 RPM performance (standardised beta=0.04; t(310)=6.63;

P<0.001) contributed significantly in a final model which as a whole accounted for approximately 16% of the total variance (R^2=16.1%; $F(4,310)$=16.07; $P<0.001$).

5.11.3. Verbal Fluency

Peak Prior Cognitive Ability-Adjusted Analysis

No analyses of the association between CVD and VFT residual scores were performed, statistically taking VFT performance scores in 1998/9 into control. Rather, the residual scores of the VFT in 2002/3 were examined in relation to stroke, in models adjusting first for age and sex, and then additionally for an estimate of peak prior cognitive ability (table 39). In neither model was stroke significantly associated with the outcome variable. Adjusting the age and sex controlled models further for peak prior ability did not have any impact on the relation between stroke and the dependent variable. In this model, which contributed only about 3% to the total variance (R^2=2.7%; $F(4,277)$=2.97; P=0.020), both age (standardised beta=0.02; $t(277)$=2.08; P=0.038) and prior ability (standardised beta=0.02; $t(277)$=2.08; P=0.010) exerted independent effects on the outcome variable.

5.11.4. Digit Symbol-Coding

Peak Prior Cognitive Ability-Adjusted Analysis

Identically to above, our analysis of the residuals of the DST in relation to CVD was limited to models adjusting for peak prior cognitive ability rather than earlier performance on the DST. In the first of these, the dependent variable was examined in relation to any CVD as well as potential confounders (see table 40). The cumulative adjustment for these (models 1 to 3 and 11 to 17) led only to a slight attenuation in the association of vascular disease with the cognitive outcome, but in none of the models was having any CVD significantly related to the DST residual scores. In the final model, which accounted for 18% of the total variance (R^2=18.0%;

F(12,241)=5.63; P<0.001), the following co-variates exerted independent influence: age (standardised beta=-0.04; t(241)=-2.90; P=0.004), sex (standardised beta=0.31; t(241)=2.27; P=0.024), scores on the estimate of peak prior ability (standardised beta=-0.03; t(241)=-4.04; P<0.001), and baseline smoking (standardised beta=-0.06; t(241)=-2.67; P=0.008).

Similar results were obtained when the relationship between intermittent claudication and the DST residual scores were studied (see table 41). In models adjusting for age and sex, then additionally for prior ability, and then finally for baseline interleukin-6 levels, intermittent claudication did not exert significant influence on the outcome variable. However, in the final model, which explained around 14% of the total variance (R^2=13.9%; F(5,215)=8.08; P<0.001), age (standardised beta=-0.04; t(215)=-3.09; P=0.002), sex (standardised beta=0.40; t(215)=3.15; P=0.002), and prior ability (standardised beta=-0.03; t(215)=-4.35; P<0.001), contributed independently to the DST residual scores.

Finally, as presented in table 42, the DST residual scores were regressed on stroke and potential confounding factors in a series of models. However, in none of the models did stroke emerge as an independent predictor of the DST residual scores. In the final model, however, age (standardised beta=-0.04; t(229)=-3.33; P=0.001), sex (standardised beta=0.28; t(229)=2.15; P=0.032), peak prior ability (standardised beta=-0.02; t(229)=-3.51; P=0.001), and pack-years of smoking at baseline in 1987/8 (standardised beta=-0.06; t(229)=-2.54; P=0.012), each contributed independently (R^2=13.4%; F(6,229)=7.09; P<0.001).

5.12. CHAPTER SUMMARY

The main aim of this chapter was to present data from the sample of 452 Edinburgh Artery Study subjects who participated in assessment of cognitive function in 2002/3 and on which the results discussed herein are based. In particular, some modest differences in baseline sociodemographic and medical characteristics were observed between participants considered eligible for cognitive testing in 2002/3 and those who were actually assessed. On the whole, the cognitively tested subjects were relatively younger, comprised relatively more males, were more educated, and of higher social standing. In addition, they also had slightly more favourable medical and lifestyle profiles. An examination of cognitive test performance in relation to CVD status showed an overall decline in mean scores on the majority of cognitive tests in both diseased and non-vascular subjects over 1998/9 to 2002/3.

In multivariate analyses, adjusting for age, sex, and prior ability, subjects with stroke scored lower on most tests compared to non-vascular controls. Further analyses demonstrated that stroke was associated with a progressive decline in general ability, verbal memory and verbal fluency. Similarly, subjects with MI but without a recognised previous stroke obtained lower scores on tests of verbal memory and non-verbal reasoning. In linear regression analyses, MI independently predicted steeper decline in non-verbal reasoning. In contrast to these findings, angina was not significantly related to cognitive decline in any of the analyses. Intermittent claudication was further associated with a significant progressive decline in both general cognitive function and verbal memory after control for possible confounders.

Several potentially modifiable vascular risk factors, including education, body mass index, smoking, diastolic blood pressure, inflammatory markers and blood viscosity were also related to decline in general and specific cognitive abilities, independently of age, sex, prior cognitive ability and vascular disease. Further analyses demonstrated that the associations with decline in specific cognitive measures principally resulted from the relationship between vascular disease and risk factors with general cognitive ability rather than the individual functions per se.

FIGURE 1. Participation in the second round of cognitive function testing in 2002/3.

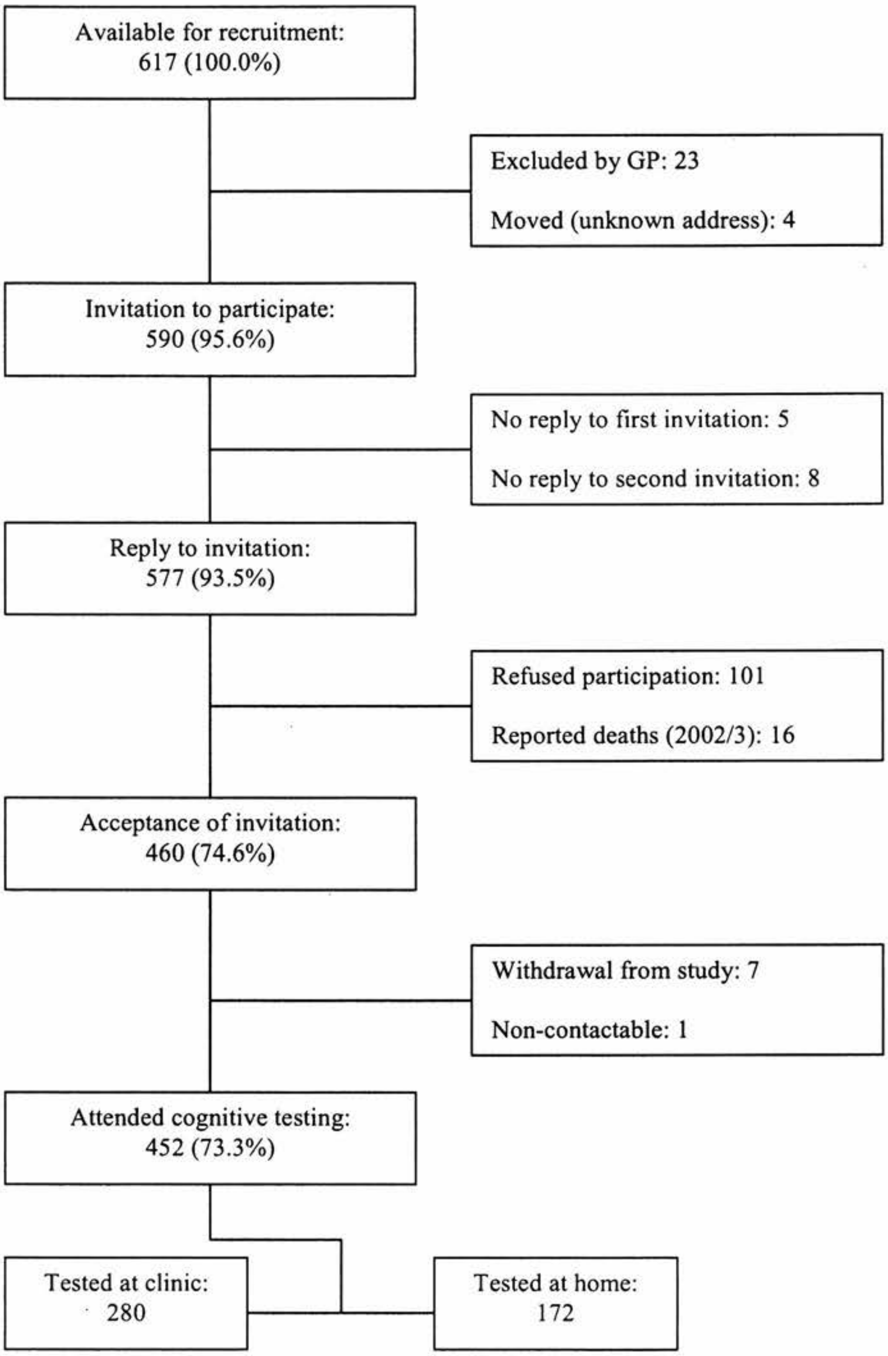


TABLE 1. Baseline sociodemographic characteristics, lifestyle, and frequency of cardiovascular disease in cognitively tested versus non-tested subjects in 2002/3.

	N	Survivors† (n=1027)	N	All Eligible Subjects‡ (n=590)	N	Tested (n=452)	N	Not Tested (n=138)
Mean Age, Years (SD)	1027	63.3 (5.3)	590	62.9 (5.1)	452	62.6 (5.0)	138	64.0 (5.4)
Male Sex % (n)		44.7 (459)		49.0 (289)		49.8 (225)		46.4 (64)
Education Level % (n)								
University		17.0 (174)		20.2 (119)		22.2 (100)		13.9 (19)
Post school training		19.3 (197)		21.9 (129)		24.8 (112)		12.4 (17)
Secondary		61.5 (629)		56.6 (333)		51.7 (233)		73.0 (110)
Primary		2.2 (23)		1.2 (7)		1.3 (6)		0.7 (1)
Social Class % (n)								
I		12.8 (131)		13.9 (82)		14.6 (66)		11.6 (16)
II		33.8 (345)		39.0 (230)		41.0 (185)		32.6 (45)
IIIN		26.6 (271)		22.9 (135)		21.1 (95)		29.0 (40)
IIIM		16.0 (163)		15.8 (93)		15.7 (71)		15.9 (22)
IV-V		10.7 (110)		8.4 (49)		6.6 (34)		10.9 (15)
Median Pack-Years of smoking (IQR)*	1009	3.7 (0.0-22.8)	583	4.0 (0.0-24.0)	446	2.7 (0.0-20.2)	137	10.0 (0.0-29.4)
Mean BMI (kg/m^2) (SD)	1027	25.6 (4.0)	590	25.6 (3.9)	452	25.6 (3.6)	138	25.6 (4.6)
Mean Systolic Blood Pressure (mmHg) (SD)	1026	141.6 (22.8)	590	140.1 (22.6)	452	138.8 (22.0)	138	144.5 (24.1)
Glucose Tolerance % (n)								
Normal		83.9 (840)		85.1 (493)		87.4 (388)		77.8 (105)
Impaired glucose tolerance		12.0 (120)		12.1 (70)		9.9 (44)		19.3 (26)
Diabetic		4.1 (41)		2.8 (16)		2.7 (12)		3.0 (4)
Cardiovascular Disease % (n)								
Myocardial infarction		2.1 (22)		2.0 (12)		2.0 (9)		2.2 (3)
Stroke		1.4 (14)		1.5 (9)		1.3 (6)		2.2 (3)

† Subjects who had survived up to the time of recruitment to cognitive testing in 2002/3 (565 subjects had died since baseline). *Includes never smokers with zero pack-years of smoking. ‡Subjects eligible for cognitive testing in 2002/3 were those who had been cognitively tested in 1998/9, were alive at the time of testing, were considered fit to participate by their general practitioner, and whose address of residence at the time of testing was known.

TABLE 2. Cognitive performance in 1998/9 in cognitively tested versus non-tested subjects in 2002/3.

Cognitive Measure	N	Survivors† (n=1027)	N	All Eligible Subjects‡ (n=590)	N	Tested (n=452)	N	Not Tested (n=138)
Mean National Adult Reading Test score (SD)	613	32.0 (9.6)	572	32.1 (9.7)	444	33.2 (9.3)	128	22.3 (10.1)
Mean Logical Memory score (SD)	610	35.4 (13.3)	573	35.7 (13.3)	447	37.0 (13.4)	126	31.0 (11.5)
Mean Raven's Progressive Matrices score (SD)	605	33.6 (9.7)	567	33.8 (9.6)	439	35.2 (9.1)	128	30.0 (10.1)
Mean Verbal Fluency Test score (SD)	619	38.4 (12.9)	581	38.7 (12.9)	447	39.5 (12.8)	134	36.0 (13.1)
Mean Digit Symbol Test score (SD)	556	40.0 (11.1)	526	40.4 (10.9)	417	41.6 (10.8)	109	35.5 (9.9)
Mean General Cognitive Factor score (SD)	549	0.04 (0.99)	519	0.08 (0.97)	411	0.20 (0.95)	108	-0.38 (0.93)

†Subjects who had survived up to the time of recruitment to cognitive testing in 2002/3 (565 subjects had died since baseline). ‡Subjects eligible for cognitive testing in 2002/3 were those who had been cognitively tested in 1998/9, were alive at the time of testing, were considered fit to participate by their GP, and whose address at the time of testing was known.

TABLE 3. Comparison of baseline sociodemographic characteristics in cognitively tested subjects with and without major CVD.

Baseline Parameter	No CVD (n=283)	Any CVD (n=149)	Angina Pectoris (n=59)	Intermittent Claudication (n=57)	Myocardial Infarction (n=50)	Stroke (n=17)
Mean Age, Years, (SD)†	77.1 (5.0)	78.4 (4.9)*	78.4 (5.0)	78.7 (4.9)*	78.3 (4.9)	79.5 (5.8)
Age Category % (n)†						
Less than 75 years	37.1 (105)	25.5 (38)	23.7 (14)	24.6 (14)	30.0 (15)	23.5 (4)
75-79	29.3 (83)	30.2 (45)	37.3 (22)	26.3 (15)	22.0 (11)	29.4 (5)
80-84	25.1 (71)	32.2 (48)	27.1 (16)	33.3 (19)	38.0 (19)	35.3 (6)
85 years and above	8.5 (24)	12.1 (18) (trend)*	11.9 (7)	15.8 (9) (trend)*	10.0 (5)	11.8 (2)
Sex % (n)						
Male	46.6 (132)	55.0 (82)	54.2 (32)	49.1 (28)	62.0 (31)*	47.1 (8)
Education % (n)						
University	25.5 (72)	16.8 (25)	13.6 (8)	17.5 (10)	16.0 (8)	17.6 (3)
Post school training	25.5 (72)	22.1 (33)	35.6 (21)	14.0 (8)	16.0 (8)	29.4 (5)
Secondary	47.9 (135)	59.1 (88)	49.2 (29)	66.7 (38)	64.0 (32)	52.9 (9)
Primary	1.1 (3)	2.0 (3)	1.7 (1)	1.8 (1) (trend)*	4.0 (2) (trend)*	0.0 (0)
Social Class % (n)						
I	16.6 (47)	9.4 (14)	11.9 (7)	8.8 (5)	6.0 (3)	29.4 (5)
II	44.5 (126)	35.6 (53)	25.4 (15)	42.1 (24)	42.0 (21)	23.5 (4)
IIIN	18.0 (51)	26.2 (39)	28.8 (17)	24.6 (14)	24.0 (12)	23.5 (4)
IIIM	16.3 (46)	16.1 (24)	20.3 (12)	12.3 (7)	16.0 (8)	5.9 (1)
IV-V	4.6 (13)	12.8 (19) (trend)**	13.6 (8) (trend)**	12.3 (7) (trend)*	12.0 (6) (trend)*	17.6 (3)

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001. †Age at the time of cognitive testing in 2002/3.

TABLE 4. Comparison of estimates of mood, cognitive status, and peak prior cognitive ability in cognitively tested subjects with and without major CVD.

Baseline Parameter	No CVD (n=283)	Any CVD (n=149)	Angina Pectoris (n=59)	Intermittent Claudication (n=57)	Myocardial Infarction (n=50)	Stroke (n=17)
Median Anxiety Score (IQR)†	4.0 (2.0-6.0)	5.0 (3.0-8.0)***	5.0 (3.0-8.0)**	5.0 (2.0-7.5)	5.5 (3.75-8.0)**	5.0 (3.0-9.50)
Anxiety Caseness % (n)						
Probable (≥ 11)	3.9 (11)	7.4 (11)	3.4 (2)	8.8 (5)	14.0 (7)	17.6 (3)
Possible (8-10)	8.9 (25)	18.1 (27)	23.7 (14)	15.8 (9)	12.0 (6)	17.6 (3)
Non-cases (≤ 7)	87.2 (245)	74.5 (111) (trend)**	72.9 (43) (trend)*	75.4 (43) (trend)*	74.0 (37) (trend)**	64.7 (11) (trend)**
Median Depression Score (IQR)†	2.0 (1.0-4.0)	4.0 (2.0-6.0)***	4.0 (2.0-6.0)**	5.0 (3.0-6.0)***	3.5 (2.0-6.0)*	4.0 (2.0-6.0)*
Depression Caseness % (n)						
Probable (≥ 11)	0.7 (2)	2.0 (3)	1.7 (1)	1.8 (1)	2.0 (1)	5.9 (1)
Possible (8-10)	5.3 (15)	9.4 (14)	11.9 (7)	7.0 (4)	6.0 (3)	5.9 (1)
Non-cases (≤ 7)	94.0 (264)	88.6 (132) (trend)*	86.4 (51)	91.2 (52)	92.0 (46)	88.2 (15)
Mini-Mental State Examination (MMSE)						
Median Score (IQR)	29.0 (27.0-29.0)	28.5 (27.0-29.0)	28.5 (27.0-29.0)	28.0 (27.0-29.0)	28.0 (27.0-29.0)	28.0 (27.0-29.0)
National Adult Reading Test (NART)						
Mean Correct Items (SD)	35.1 (8.7)	31.3 (9.4)***	31.6 (9.7)**	30.6 (9.4)**	29.8 (9.6)***	35.5 (9.2)

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001. †The range of scores on each of the two Hospital Anxiety and Depression Scale sub-scales is 0-21.

TABLE 5. Comparison of baseline lifestyle risk factors in cognitively tested subjects with and without major CVD.

Baseline Parameter	No CVD (n=283)	Any CVD (n=149)	Angina Pectoris (n=59)	Intermittent Claudication (n=57)	Myocardial Infarction (n=50)	Stroke (n=17)
Physical Activity % (n)						
None	7.4 (21)	6.7 (10)	5.1 (3)	5.3 (3)	12.0 (6)	5.9 (1)
Light (at most)	31.4 (89)	31.5 (47)	27.1 (16)	35.1 (20)	30.0 (15)	35.3 (6)
Moderate (at most)	49.1 (139)	52.3 (78)	55.9 (33)	56.1 (32)	44.0 (22)	41.2 (7)
Strenuous (at most)	12.0 (34)	9.4 (14)	11.9 (7)	3.5 (2)	14.0 (7)	17.6 (3)
Median Total Units Alcohol/Week (IQR)	4.0 (1.0-11.0)	5.0 (1.0-15.0)	4.0 (1.0-12.0)	5.0 (1.0-15.5)	4.5 (0.0-16.2)	4.0 (0.0-18.0)
Alcohol (total units consumed last week) % (n)						
None	6.0 (17)	10.1 (15)	10.2 (6)	10.5 (6)	10.0 (5)	17.6 (3)
1-2	57.8 (163)	53.7 (80)	52.5 (31)	63.2 (36)	52.0 (26)	52.9 (9)
3-4	22.3 (63)	20.1 (30)	23.7 (14)	10.5 (6)	22.0 (11)	11.8 (2)
>4	13.8 (39)	16.1 (24)	13.6 (8)	15.8 (9)	16.0 (8)	17.6 (3)
Median Pack-Years (IQR)	0.5 (0.0-18.0)	4.25 (0.0-30.0)*	1.0 (0.0-15.0)	5.0 (0.0-28.1)	10.6 (0.0-38.5)**	36.0 (0.0-40.0)**
Smoking Status % (n)						
Current	11.7 (32)	19.0 (27)	12.5 (7)	27.8 (15)	16.7 (8)	29.4 (5)
Former	40.7 (111)	40.8 (58)	42.9 (24)	29.6 (16)	52.1 (25)	41.2 (7)
Never	47.6 (130)	40.1 (57)	44.6 (25)	42.6 (23) (trend)*	31.3 (15)	29.4 (5)

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).
*P<0.05; **P<0.01; ***P<0.001.

TABLE 6. Comparison of baseline physiological risk factors in cognitively tested subjects with and without major CVD.

Baseline Parameter	No CVD (n=283)	Any CVD (n=149)	Angina Pectoris (n=59)	Intermittent Claudication (n=57)	Myocardial Infarction (n=50)	Stroke (n=17)
Mean Body Mass Index, kg/m^2, (SD)	25.1 (3.3)	26.3 (4.3)**	26.6 (5.0)*	26.2*	26.2 (3.5)*	26.1 (2.8)
Mean Glucose Level, mmol/L, (SD)†	5.6 (0.9)	5.8 (1.5)	5.9 (1.7)	5.7 (1.4)	5.7 (1.1)	5.6 (0.7)
Glucose Tolerance % (n)						
Normal	88.9 (248)	84.8 (123)	79.3 (46)	89.3 (50)	89.4 (42)	82.4 (14)
Impaired glucose tolerance	8.6 (24)	12.4 (18)	15.5 (9)	8.9 (5)	10.6 (5)	11.8 (2)
Diabetes	2.5 (7)	2.8 (4)	5.2 (3)	1.8 (1)	0.0 (0)	5.9 (1)
Mean Systolic Blood Pressure, mmHg, (SD)	134.9 (20.3)	145.6 (23.2)***	143.5 (24.5)*	146.7 (23.1)***	147.0 (21.5)***	146.5 (24.9)*
Mean Diastolic Blood Pressure, mmHg, (SD)	74.9 (11.2)	79.2 (12.4)***	78.9 (12.7)*	78.4 (11.8)*	80.0 (12.3)**	78.2 (13.4)
Mean Total Serum Cholesterol, mmol/L, (SD)	7.0 (1.2)	7.1 (1.3)	6.9 (1.3)	7.4 (1.5)	7.1 (1.3)	7.3 (1.5)
Mean High Density Lipoprotein (HDL), mmol/L, (SD)	1.5 (0.4)	1.3 (0.3)***	1.4 (0.3)***	1.3 (0.3)***	1.3 (0.3)***	1.6 (0.4)
Mean Low Density Lipoprotein (LDL), mmol/L, (SD)	5.2 (1.1)	5.5 (1.3)*	5.2 (1.2)	5.7 (1.4)**	5.5 (1.2)	5.4 (1.5)
Median Serum Lipoprotein (a) Levels, g/L, (IQR)	0.08 (0.03-0.27)	0.09 (0.04-0.24)	0.07 (0.03-0.13)	0.10 (0.03-0.31)	0.10 (0.05-0.31)	0.10 (0.03-0.15)
Mean Serum Triglyceride Levels, mmol/L, (SD)	1.5 (0.9)	1.6 (0.7)	1.6 (0.8)	1.6 (0.6)	1.6 (0.8)	1.6 (0.6)
Mean Plasma Homocysteine Levels, µmol/L, (SD)‡	11.2 (2.9)	11.9 (3.8)	10.4 (2.0)	12.8 (4.5)*	13.0 (4.8)*	10.7 (3.5)

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

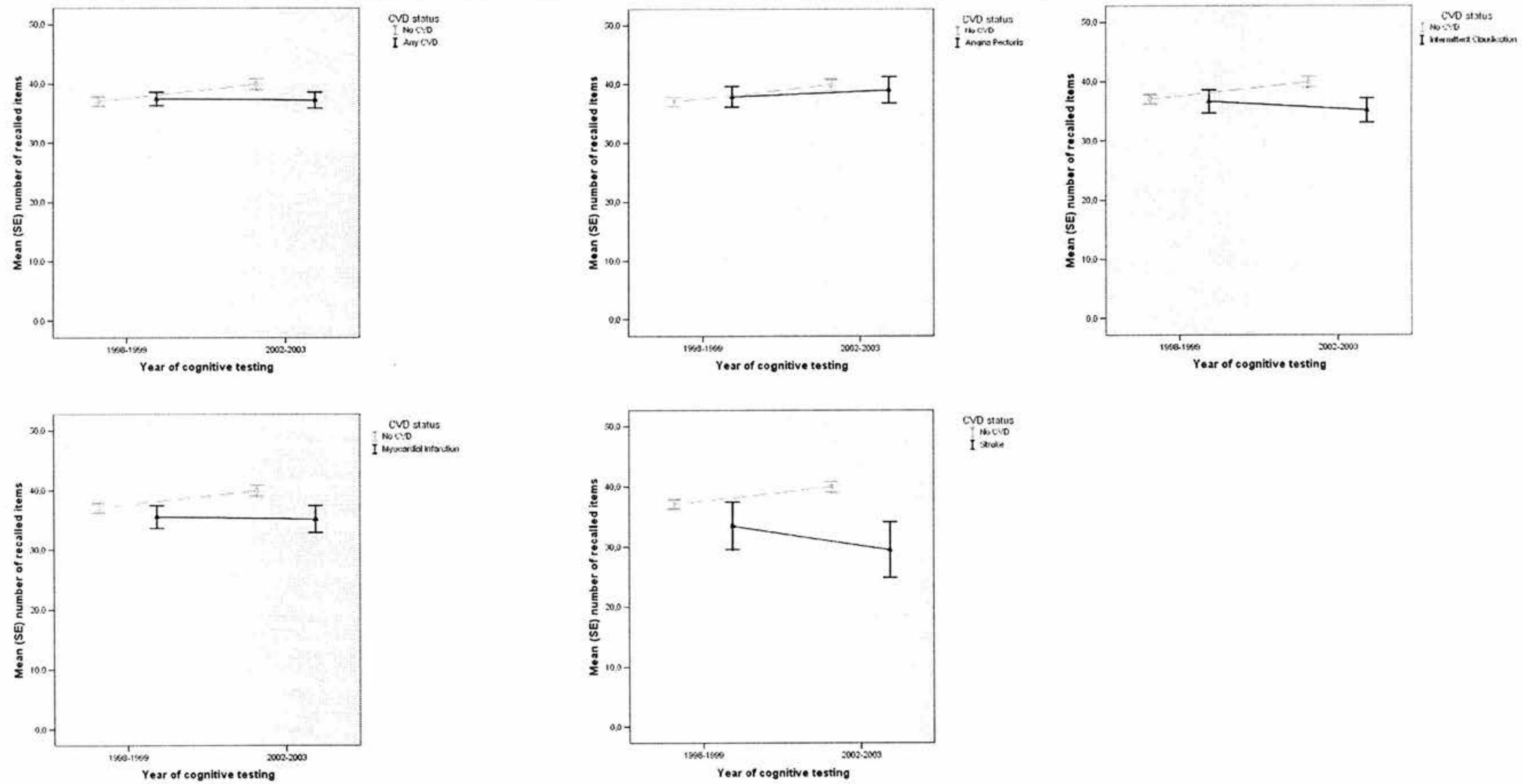
*$P<0.05$; **$P<0.01$; ***$P<0.001$. †Fasting glucose tolerance test (diabetic subjects not included). ‡Measured at 5-year follow-up examination.

TABLE 7. Comparison of baseline levels of haemostatic, inflammatory and rheological factors in cognitively tested subjects with and without major CVD.

Baseline Parameter	No CVD (n=283)	Any CVD (n=149)	Angina Pectoris (n=59)	Intermittent Claudication (n=57)	Myocardial Infarction (n=50)	Stroke (n=17)
Mean Plasma Fibrinogen Levels, g/L, (SD)	2.5 (0.6)	2.6 (0.7)**	2.6 (0.7)	2.8 (0.7)***	2.6 (0.7)	2.7 (0.5)
Mean Plasma D-Dimer Levels, µg/mL, (SD)	78.7 (46.6)	91.3 (52.7)*	85.5 (50.4)	95.5 (57.8)*	90.8 (50.9)	82.9 (33.4)
Median Serum C-Reactive Protein Levels, mg/L, (IQR)	1.1 (0.6-2.5)	1.8 (1.0-3.9)***	1.5 (1.1-2.5)*	2.5 (0.7-6.6)**	2.0 (1.1-5.2)	2.5 (1.1-9.0)*
Median Interleukin-6 Levels, pg/mL, (IQR)	1.6 (1.0-2.5)	3.4 (1.9-4.8)**	1.8 (1.4-2.9)	2.3 (1.7-4.1)***	1.9 (1.5-3.6)*	2.5 (1.3-4.8)
Mean ICAM Levels, ng/mL, (SD)	205.2 (48.8)	217.4 (48.5)*	212.5 (52.8)	225.3 (44.1)*	218.3 (46.6)	242.8 (83.6)
Mean VCAM-1 Levels, ng/mL, (SD)	362.9 (67.2)	377.0 (73.9)	384.7 (84.7)	378.2 (71.4)	367.4 (62.0)	366.9 (82.0)
Mean E-Selectin Levels, ng/mL, (SD)	39.0 (14.0)	43.2 (18.1)*	44.9 (21.6)	42.7 (14.9)	39.4 (14.9)	48.7 (24.3)
Mean Haematocrit Level, %, (SD)	45.1 (3.2)	45.9 (3.3)**	46.2 (3.3)*	45.8 (3.3)	45.8 (3.4)	46.5 (3.7)
Mean Viscosity Levels, mPa/sec (SD)						
Whole blood	3.4 (0.5)	3.6 (0.5)***	3.6 (0.6)**	3.6 (0.5)*	3.6 (0.5)*	3.7 (0.7)*
Plasma	1.30 (0.1)	1.32 (0.1)**	1.34 (0.1)**	1.33 (0.1)*	1.31 (0.1)	1.32 (0.1)

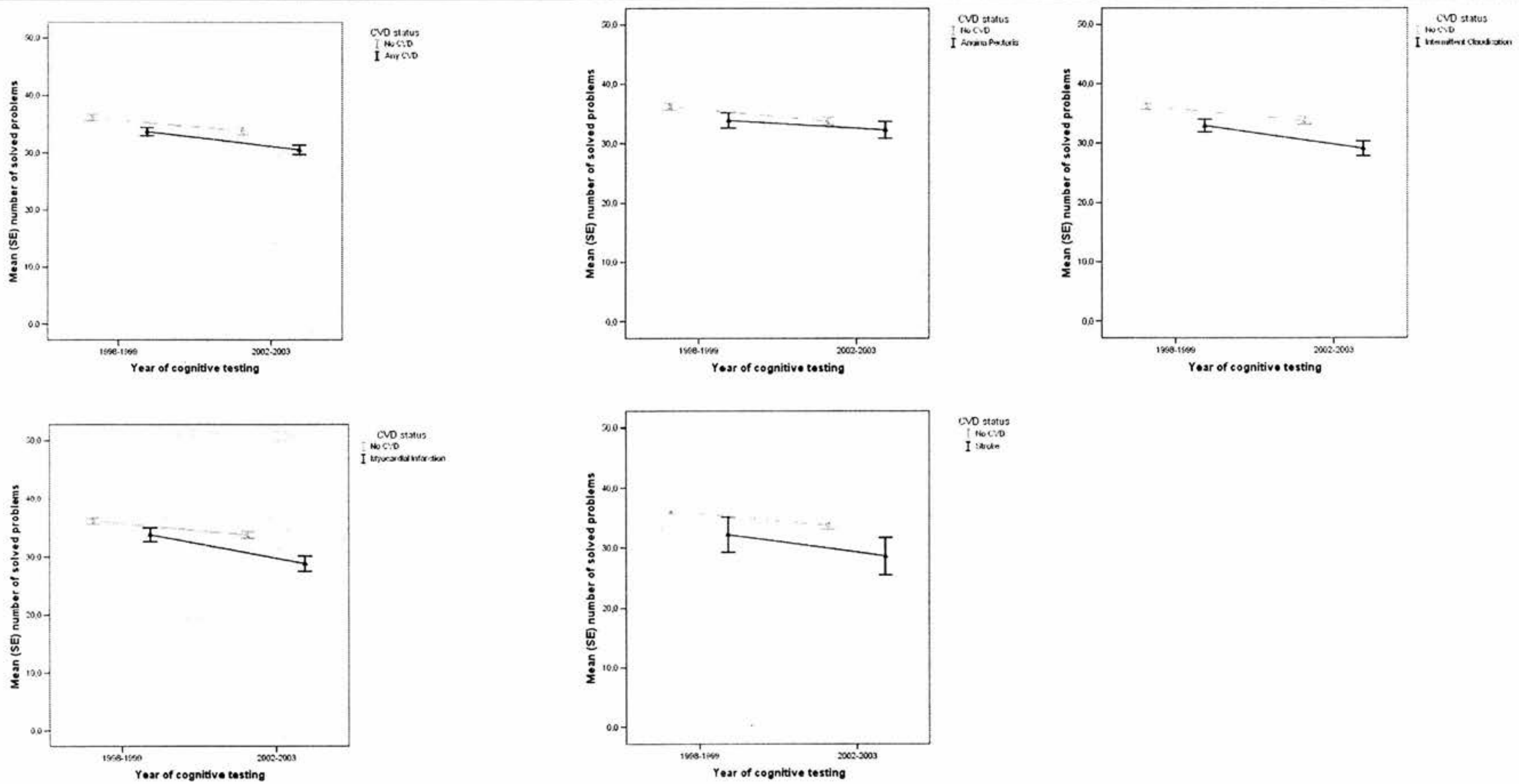
Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).
*P<0.05; **P<0.01; ***P<0.001.

FIGURE 2. Logical Memory Test performance in 1998/9 and 2002/3 in subjects with and without major CVD.



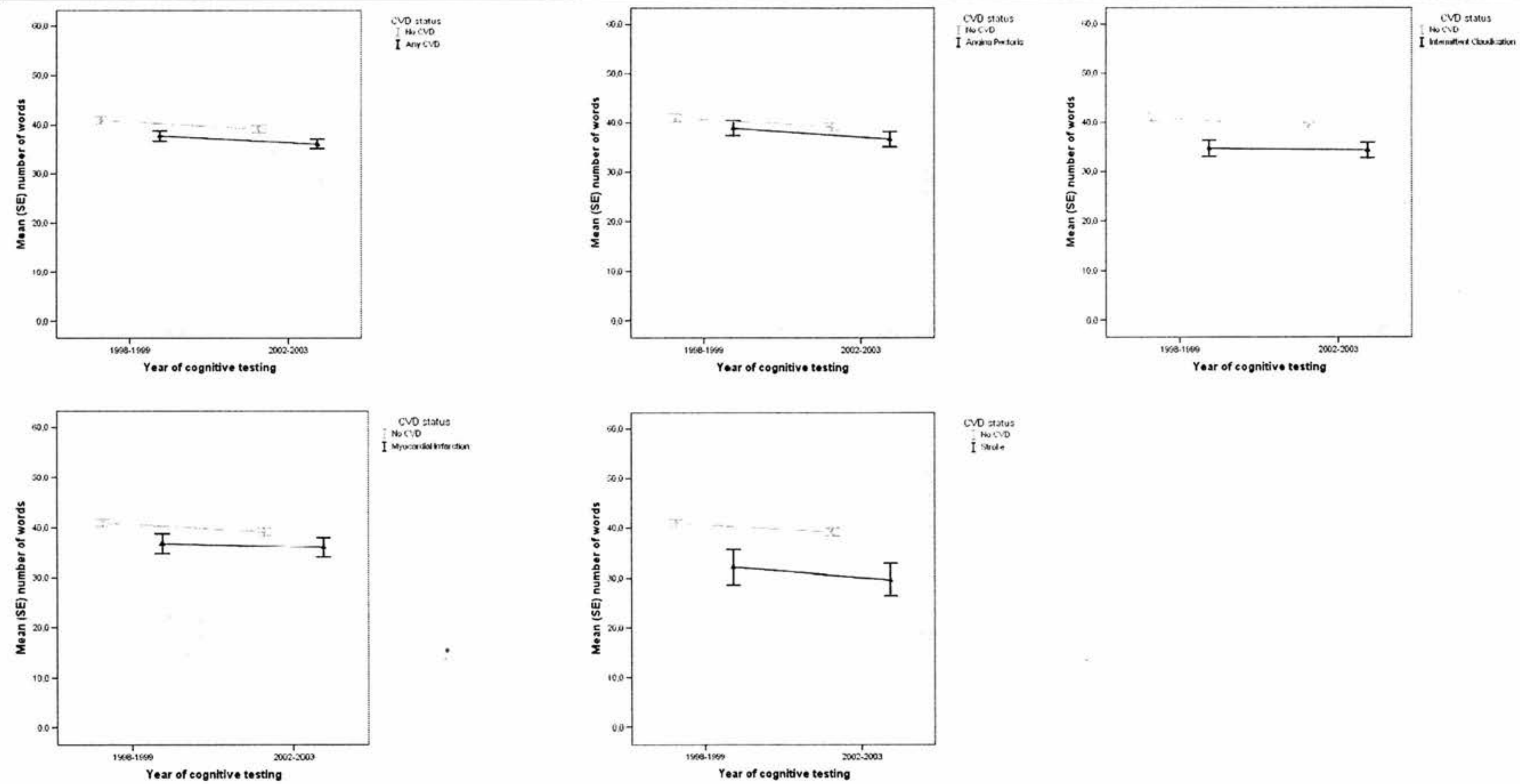
No CVD (n=283); Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

FIGURE 3. Raven's Progressive Matrices performance in 1998/9 and 2002/3 in subjects with and without major CVD.



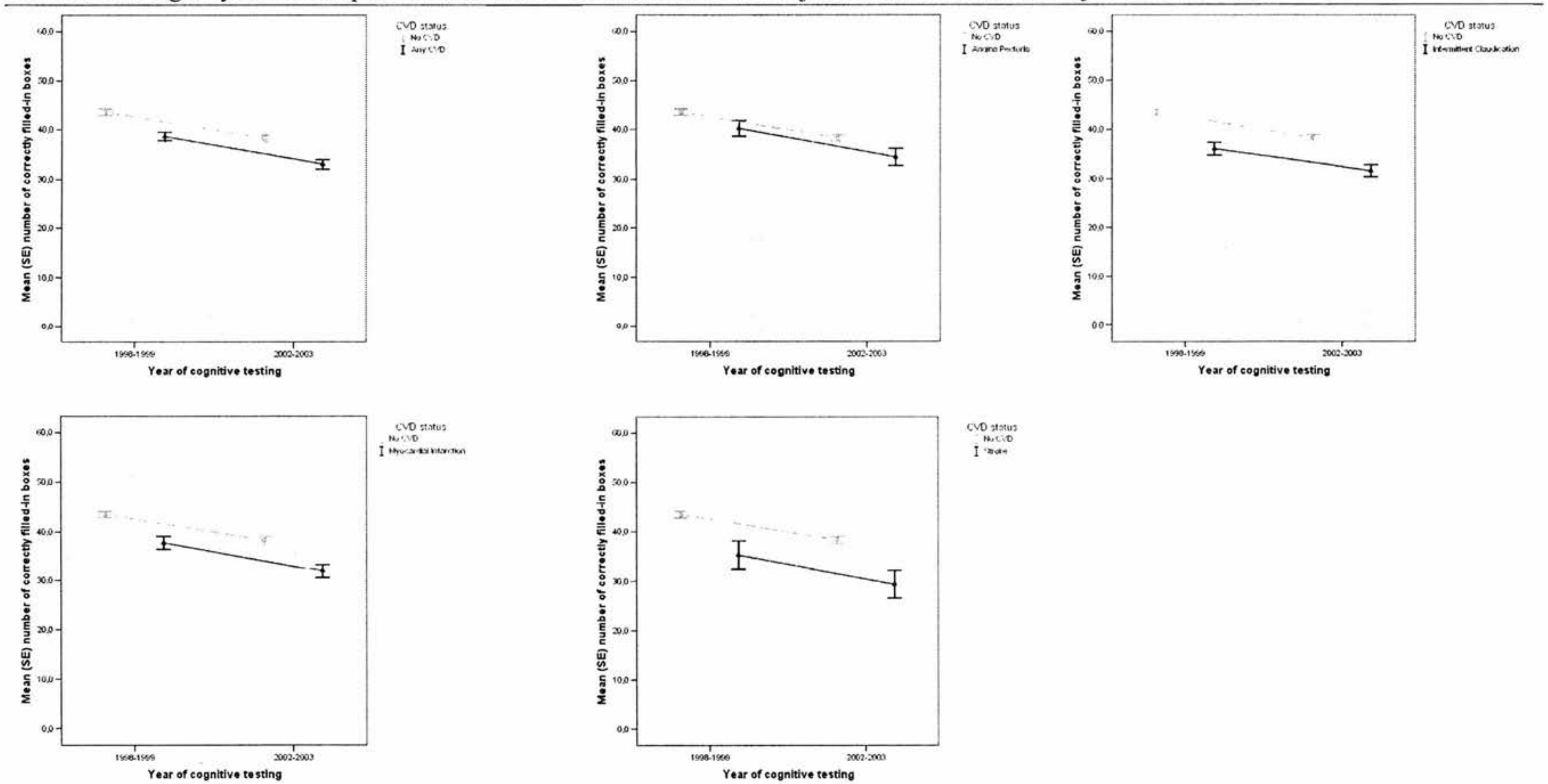
No CVD (n=283); Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

FIGURE 4. Verbal Fluency Test performance in 1998/9 and 2002/3 in subjects with and without major CVD.



No CVD (n=283); Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

FIGURE 5. Digit Symbol Test performance in 1998/9 and 2002/3 in subjects with and without major CVD.



No CVD (n=283); Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17); Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease; Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15); Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

TABLE 8. Mean differences (95% CI) in cognitive test scores in 2002/3 by CVD status, adjusted for demographic factors and cognitive performance in 1998/9.

Cognitive Measure	N	No CVD (n=283)	N	Any CVD (n=149)
Logical Memory Test				
Age & sex adjusted	277	39.7 (37.9-41.6)	148	37.6 (35.1-40.1)
Age, sex & 1998/9 score adjusted	274	40.0 (38.7-41.3)	147	37.3 (35.5-39.0)*
Raven's Progressive Matrices				
Age & sex adjusted	274	33.6 (32.4-34.7)	141	30.8 (29.2-32.3)**
Age, sex & 1998/9 score adjusted	271	33.2 (32.4-33.9)	138	32.2 (31.1-33.2)
Verbal Fluency Test				
Age & sex adjusted	280	39.0 (37.5-40.5)	146	36.6 (34.5-38.6)
Age, sex & 1998/9 score adjusted	279	38.3 (37.4-39.2)	144	38.2 (37.0-39.4)
Digit Symbol Test				
Age & sex adjusted	272	37.9 (36.6-39.2)	143	33.9 (32.1-35.6)***
Age, sex & 1998/9 score adjusted	262	37.3 (36.6-38.1)	131	36.8 (35.7-37.8)
General Cognitive Factor				
Age & sex adjusted	269	0.13 (0.02-0.24)	138	-0.17 (-0.32 to -0.01)**
Age, sex & 1998/9 score adjusted	256	0.11 (0.06-0.17)	125	0.02 (-0.06-0.11)

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 9. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with angina and no CVD, adjusted for demographic factors and cognitive performance in 1998/9.

Cognitive Measure	N	No CVD (n=283)	N	Angina Pectoris (n=59)
Logical Memory Test				
Age & sex adjusted	277	39.8 (38.0-41.6)	58	39.6 (35.7-43.6)
Age, sex & 1998/9 score adjusted	274	40.0 (38.7-41.3)	58	38.6 (35.8-41.5)
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.6-34.8)	53	32.7 (30.1-35.2)
Age, sex & 1998/9 score adjusted	271	33.7 (32.9-34.4)	51	34.2 (32.4-35.9)
Verbal Fluency Test				
Age & sex adjusted	280	39.1 (37.7-40.6)	57	37.5 (34.2-40.7)
Age, sex & 1998/9 score adjusted	279	39.0 (38.1-39.9)	56	38.3 (36.3-40.2)
Digit Symbol Test				
Age & sex adjusted	272	38.1 (36.8-39.4)	54	35.5 (32.6-38.4)
Age, sex & 1998/9 score adjusted	262	38.4 (37.6-39.1)	47	38.4 (36.7-40.1)
General Cognitive Factor				
Age & sex adjusted	269	0.15 (0.04-0.26)	52	0.04 (-0.21-0.30)
Age, sex & 1998/9 score adjusted	256	0.18 (0.12-0.23)	44	0.20 (0.07-0.34)

Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease.

*P<0.05; **P<0.01; ***P<0.001.

TABLE 10. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with intermittent claudication and no CVD, adjusted for demographic factors and cognitive performance in 1998/9.

Cognitive Measure	N	No CVD (n=283)	N	Intermittent Claudication (n=57)
Logical Memory Test				
Age & sex adjusted	277	39.8 (38.0-41.6)	57	35.9 (32.0-39.9)
Age, sex & 1998/9 score adjusted	274	39.8 (38.6-41.1)	57	35.7 (32.9-38.5)**
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.5-34.8)	55	29.8 (27.3-32.3)**
Age, sex & 1998/9 score adjusted	271	33.4 (32.6-34.2)	55	31.5 (29.8-33.2)*
Verbal Fluency Test				
Age & sex adjusted	280	39.1 (37.6-40.6)	56	34.9 (31.5-38.2)*
Age, sex & 1998/9 score adjusted	279	38.3 (37.4-39.1)	56	39.0 (37.1-40.9)
Digit Symbol Test				
Age & sex adjusted	272	38.1 (36.8-39.3)	56	32.7 (29.9-35.4)**
Age, sex & 1998/9 score adjusted	262	37.7 (37.0-38.4)	53	37.0 (35.4-38.6)
General Cognitive Factor				
Age & sex adjusted	269	0.14 (0.03-0.25)	53	-0.32 (-0.57 to -0.07)**
Age, sex & 1998/9 score adjusted	256	0.12 (0.07-0.18)	50	-0.03 (-0.15-0.10)*

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 11. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with MI and no CVD, adjusted for demographic factors and cognitive performance in 1998/9.

Cognitive Measure	**N**	**No CVD** (n=283)	**N**	**Myocardial Infarction** (n=50)
Logical Memory Test				
Age & sex adjusted	277	39.9 (38.1-41.7)	50	35.4 (31.1-39.6)
Age, sex & 1998/9 score adjusted	274	39.7 (38.5-41.0)	49	36.3 (33.2-39.4)*
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.6-34.8)	50	29.0 (26.4-31.7)**
Age, sex & 1998/9 score adjusted	271	33.5 (32.8-34.3)	49	30.9 (29.1-32.7)**
Verbal Fluency Test				
Age & sex adjusted	280	39.2 (37.6-40.7)	50	36.3 (32.7-40.0)
Age, sex & 1998/9 score adjusted	279	38.7 (37.8-39.5)	49	39.6 (37.5-41.7)
Digit Symbol Test				
Age & sex adjusted	272	38.1 (36.9-39.4)	50	33.1 (30.2-36.1)**
Age, sex & 1998/9 score adjusted	262	38.0 (37.2-38.7)	47	37.0 (35.3-38.7)
General Cognitive Factor				
Age & sex adjusted	269	0.15 (0.04-0.26)	50	-0.33 (-0.59 to –0.07)**
Age, sex & 1998/9 score adjusted	256	0.13 (0.08-0.19)	47	0.00 (-0.13-0.14)

Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 12. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with stroke and no CVD, adjusted for demographic factors and cognitive performance in 1998/9.

Cognitive Measure	N	No CVD (n=283)	N	Stroke (n=17)
Logical Memory Test				
Age & sex adjusted	277	39.9 (38.1-41.7)	17	31.0 (23.8-38.3)*
Age, sex & 1998/9 score adjusted	274	39.8 (38.5-41.1)	17	32.6 (27.3-37.8)*
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.6-34.9)	15	29.8 (25.0-34.7)
Age, sex & 1998/9 score adjusted	271	33.7 (33.0-34.5)	15	31.5 (28.2-34.7)
Verbal Fluency Test				
Age & sex adjusted	280	39.2 (37.7-40.7)	17	30.4 (24.2-36.6)**
Age, sex & 1998/9 score adjusted	279	38.8 (37.9-39.7)	16	37.6 (33.9-41.2)
Digit Symbol Test				
Age & sex adjusted	272	38.2 (37.0-39.5)	15	30.5 (25.1-35.9)**
Age, sex & 1998/9 score adjusted	262	38.5 (37.8-39.2)	11	38.5 (35.0-42.0)
General Cognitive Factor				
Age & sex adjusted	269	0.16 (0.04-0.27)	14	-0.51 (-1.0 to -0.03)**
Age, sex & 1998/9 score adjusted	256	0.18 (0.13-0.24)	10	-0.10 (-0.38-0.18)*

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 13. 1998/9 cognitive performance-adjusted regression analysis of general cognitive factor scores in 2002/3 in relation to intermittent claudication (N=306). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3	
	B	SE	B	SE	B	SE
Intermittent claudication	-0.47**	0.14	-0.15*	0.07	-0.15*	0.07
Age	-0.06***	0.01	-0.01	0.00	-0.01	0.00
Sex	-0.10	0.10	-0.04	0.05	-0.04	0.05
GCF *(1998/9)*			0.83***	0.03	0.84***	0.03
BMI					-0.01*	0.01
R^2	0.146		0.795		0.797	
Df	(3, 302)		(4, 301)		(5, 300)	
F	18.44***		296.88***		240.80***	
ΔR^2			0.643		0.003	
Df			(1, 301)		(1, 300)	
F			957.11***		4.12*	

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 14. 1998/9 cognitive performance-adjusted regression analysis of general cognitive factor scores in 2002/3 in relation to stroke (N=266). Numbers are unstandardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**	
	B	SE	B	SE
Stroke	-0.46	0.29	-0.29*	0.14
Age	-0.07***	0.01	-0.01	0.01
Sex	-0.12	0.11	-0.04	0.05
GCF *(1998/9)*			0.84***	0.03
R^2	0.136		0.788	
Df	(3, 262)		(4, 261)	
F	14.89***		247.23***	
ΔR^2			0.646	
Df			(1, 261)	
F			806.87***	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 15. Mean differences (95% CI) in cognitive test scores in 2002/3 by CVD status, adjusted for demographic factors and peak prior cognitive ability.

Cognitive Measure	N	No CVD (n=283)	N	Any CVD (n=149)
Logical Memory Test				
Age & sex adjusted	277	39.7 (37.9-41.6)	148	37.6 (35.1-40.1)
Age, sex & NART adjusted	275	39.1 (37.3-40.8)	145	39.1 (36.7-41.6)
Raven's Progressive Matrices				
Age & sex adjusted	274	33.6 (32.4-34.7)	141	30.8 (29.2-32.3)**
Age, sex & NART adjusted	273	33.0 (32.0-33.9)	140	32.0 (30.6-33.4)
Verbal Fluency Test				
Age & sex adjusted	280	39.0 (37.5-40.5)	146	36.6 (34.5-38.6)
Age, sex & NART adjusted	277	38.3 (37.0-39.6)	144	38.1 (36.3-40.0)
Digit Symbol Test				
Age & sex adjusted	272	37.9 (36.6-39.2)	143	33.9 (32.1-35.6)***
Age, sex & NART adjusted	271	37.4 (36.2-38.5)	142	35.0 (33.4-36.7)*
General Cognitive Factor				
Age & sex adjusted	269	0.13 (0.02-0.24)	138	-0.17 (-0.32 to –0.01)**
Age, sex & NART adjusted	268	0.07 (-0.02-0.16)	138	-0.03 (-0.16-0.09)

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 16. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with angina and no CVD, adjusted for demographic factors and peak prior cognitive ability.

Cognitive Measure	N	No CVD (n=283)	N	Angina Pectoris (n=59)
Logical Memory Test				
Age & sex adjusted	277	39.8 (38.0-41.6)	58	39.6 (35.7-43.6)
Age, sex & NART adjusted	275	39.6 (37.9-41.3)	56	41.3 (37.5-45.1)
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.6-34.8)	53	32.7 (30.1-35.2)
Age, sex & NART adjusted	273	33.5 (32.5-34.5)	53	34.0 (31.8-36.2)
Verbal Fluency Test				
Age & sex adjusted	280	39.1 (37.7-40.6)	57	37.5 (34.2-40.7)
Age, sex & NART adjusted	277	39.0 (37.7-40.3)	55	38.8 (35.8-41.7)
Digit Symbol Test				
Age & sex adjusted	272	38.1 (36.8-39.4)	54	35.5 (32.6-38.4)
Age, sex & NART adjusted	271	37.9 (36.7-39.1)	54	36.7 (34.0-39.4)
General Cognitive Factor				
Age & sex adjusted	269	0.15 (0.04-0.26)	52	0.04 (-0.21-0.30)
Age, sex & NART adjusted	268	0.13 (0.04-0.22)	52	0.16 (-0.04-0.37)

Angina (n=59) includes those with angina and no other known clinical manifestation of cardiovascular disease.

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 17. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with intermittent claudication and no CVD, adjusted for demographic factors and peak prior cognitive ability.

Cognitive Measure	N	No CVD (n=283)	N	Intermittent Claudication (n=57)
Logical Memory Test				
Age & sex adjusted	277	39.8 (38.0-41.6)	57	35.9 (32.0-39.9)
Age, sex & NART adjusted	275	39.3 (37.7-41.0)	56	38.6 (34.9-42.3)
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.5-34.8)	55	29.8 (27.3-32.3)**
Age, sex & NART adjusted	273	33.3 (32.4-34.2)	54	31.8 (29.7-33.9)
Verbal Fluency Test				
Age & sex adjusted	280	39.1 (37.6-40.6)	56	34.9 (31.5-38.2)*
Age, sex & NART adjusted	277	38.7 (37.4-40.0)	56	37.5 (34.6-40.5)
Digit Symbol Test				
Age & sex adjusted	272	38.1 (36.8-39.3)	56	32.7 (29.9-35.4)**
Age, sex & NART adjusted	271	37.8 (36.6-38.9)	55	34.5 (32.0-37.1)*
General Cognitive Factor				
Age & sex adjusted	269	0.14 (0.03-0.25)	53	-0.32 (-0.57 to –0.07)**
Age, sex & NART adjusted	268	0.10 (0.02-0.19)	53	-0.08 (-0.28-0.11)

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 18. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with MI and no CVD, adjusted for demographic factors and peak prior cognitive ability.

Cognitive Measure	N	No CVD (n=283)	N	Myocardial Infarction (n=50)
Logical Memory Test				
Age & sex adjusted	277	39.9 (38.1-41.7)	50	35.4 (31.1-39.6)
Age, sex & NART adjusted	275	39.5 (37.8-41.2)	50	38.1 (34.1-42.2)
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.6-34.8)	50	29.0 (26.4-31.7)**
Age, sex & NART adjusted	273	33.3 (32.3-34.2)	50	31.6 (29.3-33.8)
Verbal Fluency Test				
Age & sex adjusted	280	39.2 (37.6-40.7)	50	36.3 (32.7-40.0)
Age, sex & NART adjusted	277	38.7 (37.4-40.0)	50	39.8 (36.6-43.0)
Digit Symbol Test				
Age & sex adjusted	272	38.1 (36.9-39.4)	50	33.1 (30.2-36.1)**
Age, sex & NART adjusted	271	37.8 (36.6-38.9)	50	35.3 (32.5-38.0)
General Cognitive Factor				
Age & sex adjusted	269	0.15 (0.04-0.26)	50	-0.33 (-0.59 to –0.07)**
Age, sex & NART adjusted	268	0.10 (0.01-0.19)	50	-0.04 (-0.25-0.16)

Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 19. Mean differences (95% CI) in cognitive test scores in 2002/3 between subjects with stroke and no CVD, adjusted for demographic factors and peak prior cognitive ability.

Cognitive Measure	N	No CVD (n=283)	N	Stroke (n=17)
WMS-R Logical Memory				
Age & sex adjusted	277	39.9 (38.1-41.7)	17	31.0 (23.8-38.3)*
Age, sex & NART adjusted	275	39.9 (38.3-41.6)	16	31.9 (24.9-38.9)*
Raven's Progressive Matrices				
Age & sex adjusted	274	33.7 (32.6-34.9)	15	29.8 (25.0-34.7)
Age, sex & NART adjusted	273	33.8 (32.8-34.8)	15	29.8 (25.7-34.0)
Verbal Fluency Test				
Age & sex adjusted	280	39.2 (37.7-40.7)	17	30.4 (24.2-36.6)**
Age, sex & NART adjusted	277	39.3 (38.0-40.7)	16	31.7 (26.2-37.3)**
WAIS-R Digit Symbol Test				
Age & sex adjusted	272	38.2 (37.0-39.5)	15	30.5 (25.1-35.9)**
Age, sex & NART adjusted	271	38.3 (37.1-39.4)	14	31.8 (26.7-36.8)*
General Cognitive Factor				
Age & sex adjusted	269	0.16 (0.04-0.27)	14	-0.51 (-1.0 to –0.03)**
Age, sex & NART adjusted	268	0.16 (0.08-0.25)	14	-0.54 (-0.9 to –0.16)***

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 20. Peak prior cognitive ability-adjusted regression analysis of general cognitive factor scores in 2002/3 in relation to stroke (N=238). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3	
	B	SE	B	SE	B	SE
Stroke	-0.52	0.32	-0.70**	0.25	-0.59*	0.25
Age	-0.08***	0.01	-0.07***	0.01	-0.07***	0.01
Sex	-0.09	0.12	-0.07	0.10	-0.14	0.10
NART			0.06***	0.00	0.06***	0.00
Blood Viscosity					-0.22*	0.10
R^2	0.147		0.464		0.473	
Df	(3, 234)		(4, 233)		(5, 232)	
F	14.61***		52.20***		43.57***	
ΔR^2			0.315		0.012	
Df			(1, 233)		(1, 232)	
F			139.11***		5.24*	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 21. 1998/9 cognitive performance-adjusted regression analysis of Logical Memory Test scores in 2002/3 in relation to any CVD (N=409). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5	
	B	SE	B	SE	B	SE	B	SE	B	SE
Any CVD	-2.26	1.59	-2.67*	1.14	-2.19	1.15	-3.04**	1.15	-2.56*	1.15
Age	-0.50**	0.15	-0.15	0.11	-0.17	0.11	-0.20	0.11	-0.23*	0.11
Sex	-1.63	1.50	-0.50	1.08	0.01	1.09	-0.85	1.09	-0.34	1.09
LMT *(1998/9)*			0.80***	0.04	0.77***	0.04	0.80***	0.04	0.77**	0.04
Education					-1.86**	0.68	---		-1.95**	0.68
Fibrinogen							2.10*	0.92	2.25*	0.91
R^2	0.029		0.499		0.507		0.504		0.513	
Df	(3, 405)		(4, 404)		(5, 403)		(5, 403)		(6, 402)	
F	5.13**		102.51***		84.79***		83.90***		72.56***	
ΔR^2			0.467		0.009		0.006		0.016	
Df			(1, 404)		(1, 403)		(1, 403)		(2, 402)	
F			380.21***		7.40**		5.21*		6.80**	

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 22. 1998/9 cognitive performance-adjusted regression analysis of Logical Memory Test scores in 2002/3 in relation to intermittent claudication (N=323). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Intermittent claudication	-3.63	2.17	-4.01*	1.57	-3.29*	1.57	-3.68*	1.58	-4.78**	1.60	-2.92	1.57	-3.72*	1.59
Age	-0.54**	0.17	-0.13	0.12	-0.17	0.12	-0.11	0.12	-0.17	0.12	-0.16	0.12	-0.21	0.12
Sex	-1.39	1.65	-1.08	1.19	-0.50	1.19	-1.15	1.19	-1.55	1.20	-0.56	1.18	-1.04	1.19
LMT *(1998/9)*			0.77***	0.04	0.74***	0.05	0.78***	0.04	0.78***	0.04	0.74***	0.05	0.74***	0.05
Education					-2.40**	0.74	---		---		-2.46**	0.73	-2.56***	0.73
Diastolic pressure							-0.10	0.05	---		-0.10*	0.05	-0.10*	0.05
Fibrinogen									2.55*	1.06			2.71**	1.04
R^2	0.036		0.494		0.509		0.498		0.502		0.514		0.523	
Df	(3, 319)		(4, 318)		(5, 317)		(5, 317)		(5, 317)		(6, 316)		(7, 315)	
F	5.06**		79.71***		67.84***		65.00***		65.90***		57.79***		51.42***	
ΔR^2			0.455		0.016		0.006		0.009		0.006		0.010	
Df			(1, 318)		(1, 317)		(1, 317)		(1, 317)		(1, 316)		(1, 315)	
F			289.92***		10.67**		3.56		5.81*		4.14*		6.84**	

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 23. 1998/9 cognitive performance-adjusted regression analysis of Logical Memory Test scores in 2002/3 in relation to MI (N=322). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3	
	B	SE	B	SE	B	SE
MI	-4.31	2.32	-3.36*	1.69	-2.80	1.69
Age	-0.50**	0.17	-0.14	0.12	-0.17	0.12
Sex	-2.65	1.67	-1.81	1.21	-1.34	1.22
LMT *(1998/9)*			0.79***	0.05	0.76***	0.05
Education					-1.71*	0.75
R^2	0.036		0.492		0.499	
Df	(3, 318)		(4, 317)		(5, 316)	
F	4.99**		78.75***		64.90***	
ΔR^2			0.453		0.008	
Df			(1, 317)		(1, 316)	
F			286.58***		5.26*	

Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 24. 1998/9 cognitive performance-adjusted regression analysis of Logical Memory Test scores in 2002/3 in relation to stroke (N=291). Numbers are unstandardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**	
	B	SE	B	SE
Stroke	-8.74*	3.72	-7.17*	2.75
Age	-0.70***	0.17	-0.17	0.13
Sex	-1.32	1.74	-1.26	1.28
LMT *(1998/9)*			0.77***	0.05
R^2	0.069		0.491	
Df	(3, 287)		(4, 286)	
F	8.16***		70.98***	
ΔR^2			0.420	
Df			(1, 286)	
F			239.14***	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 25. Peak prior cognitive ability-adjusted regression analysis of Logical Memory Test scores in 2002/3 in relation to stroke (N=205). Numbers are unstandardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**		**Model 3**	
	B	SE	B	SE	B	SE
Stroke	-2.43	5.01	-3.25	4.60	-5.78	4.51
Age	-0.73***	0.21	-0.78***	0.19	-0.94***	0.19
Sex	-2.01	2.17	-2.22	1.99	-1.99	1.93
NART			0.70***	0.11	0.76***	0.11
CRP					3.84***	1.03
R^2	0.044		0.197		0.246	
Df	(3, 201)		(4, 200)		(5, 199)	
F	4.16**		13.49***		14.28***	
ΔR^2			0.154		0.052	
Df			(1, 200)		(1, 199)	
F			39.12***		13.96***	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability)

TABLE 26. 1998/9 cognitive performance-adjusted regression of Raven's Progressive Matrices scores in 2002/3 in relation to intermittent claudication (N=217). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Intermittent claudication	-3.20	1.70	-1.39	1.16	-1.06	1.17	-1.28	1.16	-1.23	1.17	-1.24	1.16	-0.98	1.17	-0.89	1.17	-0.79	1.17
Age	-0.60***	0.13	-0.27**	0.09	-0.31**	0.09	-0.25**	0.09	-0.25**	0.09	-0.26**	0.09	-0.29**	0.09	-0.28**	0.09	-0.27**	0.09
Sex	-3.38*	1.32	-1.52	0.91	-1.32	0.91	-1.32	0.91	-1.42	0.91	-1.97*	0.93	-1.14	0.91	-1.11	0.91	-1.53	0.95
RPM *(1998/9)*			0.82***	0.05	0.78***	0.05	0.81***	0.05	0.80***	0.05	0.80***	0.05	0.78***	0.05	0.77***	0.06	0.76***	0.06
Education					-1.16*	0.58	---		---		---		-1.10	0.58	-1.09	0.58	-1.04	0.58
Fibrinogen							-1.28	0.87	---		---		-1.16	0.87	-0.91	0.90	-0.77	0.90
ICAM-1									-0.01	0.01	---		---		-0.01	0.01	-0.01	0.01
Blood Viscosity											-1.94	0.99	---		---		-1.64	1.00
R^2	0.122		0.591		0.597		0.593		0.593		0.597		0.598		0.598		0.602	
Df	(3, 213)		(4, 212)		(5, 211)		(5, 211)		(5, 211)		(5, 211)		(6, 210)		(7, 209)		(8, 208)	
F	11.02***		79.10***		64.96***		64.05***		63.95***		64.88***		54.64***		46.98***		41.78***	
ΔR^2			0.464		0.007		0.004		0.004		0.007		0.003		0.002		0.005	
Df			(1, 212)		(1, 211)		(1, 211)		(1, 211)		(1, 211)		(1, 210)		(1, 209)		(1, 208)	
F			245.41***		3.97*		2.15		1.94		3.81		1.79		1.02		2.69	

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15). *P<0.05; **P<0.01; ***P<0.001.

TABLE 27. 1998/9 cognitive performance-adjusted regression analysis of Raven's Progressive Matrices scores in 2002/3 in relation to MI (N=320). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2	
	B	SE	B	SE
MI	-4.58**	1.46	-2.65**	0.98
Age	-0.58***	0.11	-0.22**	0.07
Sex	-3.78***	1.05	-1.09	0.72
RPM *(1998/9)*			0.81***	0.04
R^2	0.132		0.611	
Df	(3, 316)		(4, 315)	
F	17.23***		126.04***	
ΔR^2			0.475	
Df			(1, 315)	
F			389.02***	

Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 28. Peak prior cognitive ability-adjusted regression analysis of Verbal Fluency Test scores in 2002/3 in relation to stroke (N=293). Numbers are unstandardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**	
	B	SE	B	SE
Stroke	-7.28*	3.31	-7.61**	2.90
Age	-0.34*	0.15	-0.32*	0.13
Sex	-0.93	1.49	-0.36	1.31
NART			0.71***	0.07
R^2	0.029		0.256	
Df	(3, 289)		(4, 288)	
F	3.90**		26.17***	
ΔR^2			0.228	
Df			(1, 288)	
F			89.43***	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 29. Peak prior cognitive ability-adjusted regression analysis of Digit Symbol Test scores in 2002/3 in relation to any CVD (N=257). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9		Model 10	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Any CVD	-3.15*	1.35	-1.82	1.27	-1.63	1.28	-1.66	1.29	-1.55	1.25	-1.35	1.05	-1.63	1.26	-1.16	1.26	-1.72*	1.26	-1.58	1.27
Age	-1.06***	0.13	-1.08***	0.12	-1.07***	0.12	-1.06***	0.12	-1.09***	0.12	-0.97***	0.13	-1.05***	0.12	-0.97***	0.12	-1.08***	0.12	-1.06***	0.12
Sex	1.94	1.31	1.70	1.21	1.89	1.22	1.73	1.21	0.85	1.23	2.02	1.21	1.58	1.21	1.26	1.20	0.46	1.33	0.96	1.26
NART			0.45***	0.07	0.44***	0.07	0.45***	0.07	0.46***	0.07	0.43***	0.07	0.44***	0.07	0.42***	0.07	0.45***	0.07	0.43***	0.07
Anxiety Score (*N+1 Log transformed*)					-2.64	2.21	---		---		---		---		---		---		---	
Depression Score (*N+1 log transformed*)							-1.68	2.60	---		---		---		---		---		---	
Pack-Year (*Square root transformed*)									-0.72**	0.24	---		---		---		---		---	
Systolic Pressure											-0.07*	0.03	---		---		---		---	
Diastolic Pressure													-0.10*	0.05	---		---		---	
Interleukin-6 (*Log transformed*)															-3.45**	1.08	---		---	
Haematocrit																	-0.46*	0.21	---	
Blood Viscosity																			-2.56*	1.24
R^2	0.226		0.338		0.339		0.336		0.359		0.349		0.346		0.361		0.348		0.346	
Df	(3, 253)		(4, 252)		(5, 251)		(5, 251)		(5, 251)		(5, 251)		(5, 251)		(5, 251)		(5, 251)		(5, 251)	
F	25.90***		33.63***		27.24***		26.92***		29.65***		28.46***		28.07***		29.91***		28.33***		28.11***	
ΔR^2			0.113		0.004		0.001		0.023		0.014		0.011		0.025		0.013		0.011	
Df			(1, 252)		(1, 251)		(1, 251)		(1, 251)		(1, 251)		(1, 251)		(1, 251)		(1, 251)		(1, 251)	
F			43.70***		1.43		0.41		9.30**		5.42*		4.16*		10.14**		4.99*		4.28*	

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17).
*P<0.05; **P<0.01; ***P<0.001. NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 29 (cont.)

Model Term	Model 11		Model 12		Model 13		Model 14		Model 15		Model 16		Model 17	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Any CVD	-1.60	1.30	-1.44	1.28	-0.86	1.29	-0.90	1.29	-0.34	1.29	-0.37	1.29	-0.37	1.29
Age	-1.07***	0.12	-1.09***	0.12	-0.96***	0.13	-0.97***	0.13	-0.87***	0.14	-0.88***	0.14	-0.88***	0.14
Sex	1.88	1.22	1.01	1.24	1.38	1.24	1.26	1.26	1.07	1.24	0.55	1.33	0.55	1.34
NART	0.44***	0.07	0.45***	0.07	0.43***	0.07	0.43***	0.07	0.41***	0.07	0.41***	0.06	0.41***	0.07
Anxiety Score (*N+1 Log transformed*)	-2.48	2.44	-1.80	2.41	-1.99	2.39	-2.02	2.40	-2.86	2.38	-2.96	2.38	-2.97	2.39
Depression Score (*N+1 log transformed*)	-0.44	2.87	0.09	2.83	-0.59	2.82	-0.44	2.83	0.40	2.81	0.59	2.81	0.60	2.83
Pack-Year (*Square root transformed*)			-0.70**	0.24	-0.69**	0.24	-0.69**	0.24	-0.59*	0.24	-0.55	0.24	-0.55*	0.24
Systolic Pressure					-0.07*	0.03	-0.06	0.04	-0.06	0.04	-0.06	0.04	-0.06	0.04
Diastolic Pressure							-0.04	0.06	-0.02	0.06	-0.02	0.06	-0.02	0.06
Interleukin-6 (*Log transformed*)									-3.15**	1.09	-2.95**	1.10	-2.94*	1.13
Haematocrit											-0.22	0.21	-0.21	0.25
Blood Viscosity													-0.08	1.58
R^2	0.336		0.355		0.368		0.367		0.385		0.385		0.383	
Df	(6, 250)		(7, 249)		(8, 248)		(9, 247)		(10, 246)	(11, 245)	(12, 244)			
F	22.61***		21.16***		19.66***		17.46***		17.03***		15.59***		14.23***	
ΔR^2	0.000		0.021		0.015		0.001		0.020		0.003		0.000	
Df	(1, 250)		(1, 249)		(1, 248)		(1, 247)		(1, 246)		(1, 245)		(1, 244)	
F	0.02		8.40**		6.11*		0.34		8.41**		1.10		0.00	

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17).

*P<0.05; **P<0.01; ***P<0.001. NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 30. Peak prior cognitive ability-adjusted regression analysis of Digit Symbol Test scores in 2002/3 in relation to intermittent claudication (N=224). Numbers are unstandardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3	
	B	SE	B	SE	B	SE
Intermittent claudication	-5.12**	1.88	-3.23	1.77	-2.25	1.80
Age	-0.95***	0.14	-0.98***	0.13	-0.91***	0.13
Sex	1.28	1.41	0.67	1.31	0.28	1.31
NART			0.45***	0.07	0.45***	0.07
Interleukin-6 *(Log transformed)*					-2.74*	1.20
R^2		0.198	0.314		0.327	
Df		(3, 220)	(4, 219)		(5, 218)	
F		19.34***	26.49***		22.65***	
ΔR^2			0.117		0.016	
Df			(1, 219)		(1, 218)	
F			38.16***		5.23*	

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 31. Peak prior cognitive ability-adjusted regression analysis of Digit Symbol Test scores in 2002/3 in relation to stroke (N=238). Numbers are unstandardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
	B	SE	B	SE	B	SE	B	SE	B	SE
Stroke	-5.84	3.81	-6.61	3.49	-5.26	3.49	-4.88	3.51	-3.90	3.51
Age	-1.01***	0.14	-0.99***	0.13	-0.99***	0.13	-0.98***	0.13	-0.99***	0.12
Sex	1.38	1.37	1.56	1.26	0.81	1.28	0.62	1.30	0.08	1.31
NART			0.47***	0.07	0.48***	0.07	0.45***	0.07	0.45***	0.07
Pack-Year *(Square root transformed)*					-0.67*	0.26	---		-0.59*	0.26
Blood Viscosity							-3.38**	1.28	-2.97*	1.28
R^2	0.191		0.318		0.335		0.335		0.347	
Df	(3, 234)		(4, 233)		(5, 232)		(5, 232)		(6, 231)	
F	19.64***		28.68***		24.83***		24.91***		21.98***	
ΔR^2			0.129		0.019		0.019		0.014	
Df			(1, 233)		(1, 232)		(1, 232)		(1, 231)	
F			44.77***		6.66*		6.91**		5.11*	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 32. 1998/9 cognitive performance-adjusted regression analysis of 2002/3 Logical Memory Test score residuals in relation to any CVD (N=391). Numbers are standardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5	
	B	SE	B	SE	B	SE	B	SE	B	SE
Any CVD	0.14	0.11	0.10	0.09	0.08	0.09	0.05	0.09	0.03	0.09
Age	0.01	0.01	0.03***	0.01	0.03***	0.01	0.03**	0.01	0.03**	0.01
Sex	0.01	0.10	0.05	0.09	0.03	0.09	0.01	0.09	-0.00	0.09
LMT *(1998/9)*			0.04***	0.00	0.04***	0.00	0.04***	0.00	0.04***	0.00
Education					0.07	0.05	---		0.06	0.05
Fibrinogen							0.24**	0.07	0.23**	0.07
R^2	0.001		0.262		0.264		0.281		0.282	
Df	(3, 387)		(4, 386)		(5, 385)		(5, 385)		(6, 384)	
F	1.13		35.64***		28.95***		31.45***		26.48***	
ΔR^2			0.261		0.004		0.020		0.003	
Df			(1, 386)		(1, 385)		(1, 385)		(1, 384)	
F			137.97***		1.87		10.97**		1.46	

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17). *P<0.05; **P<0.01; ***P<0.001

TABLE 33. 1998/9 cognitive performance-adjusted regression analysis of 2002/3 Logical Memory Test score residuals in relation to intermittent claudication (N=311). Numbers are standardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Intermittent claudication	0.11	0.14	0.08	0.13	0.06	0.13	0.10	0.13	0.01	0.13	0.08	0.13	0.01	0.13
Age	0.01	0.01	0.03**	0.01	0.03**	0.01	0.03**	0.01	0.02*	0.01	0.03**	0.01	0.03*	0.01
Sex	-0.03	0.11	-0.01	0.10	-0.02	0.10	-0.02	0.10	-0.05	0.10	-0.02	0.10	-0.06	0.10
LMT *(1998/9)*			0.03***	0.00	0.03***	0.00	0.03***	0.00	0.03***	0.00	0.03***	0.00	0.04***	0.00
Education					0.04	0.06	---		---		0.04	0.06	0.03	0.06
Diastolic pressure							-0.00	0.00	---		-0.00	0.00	-0.00	0.00
Fibrinogen									0.24**	0.08			0.24**	0.08
R^2	0.010		0.212		0.211		0.214		0.230		0.212		0.229	
Df	(3, 307)		(4, 306)		(5, 305)		(5, 305)		(5, 305)		(6, 304)		(7, 303)	
F	0.35		21.88***		17.59***		17.85***		19.49***		14.90***		14.17***	
ΔR^2			0.219		0.001		0.004		0.020		0.004		0.019	
Df			(1, 306)		(1, 305)		(1, 305)		(1, 305)		(1, 304)		(1, 303)	
F			86.18***		0.56		1.57		7.94**		1.49		7.65**	

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001

TABLE 34. 1998/9 cognitive performance-adjusted regression analysis of 2002/3 Logical Memory Test score residuals in relation to MI (N=314). Numbers are standardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**		**Model 3**	
	B	SE	B	SE	B	SE
MI	0.03	0.15	0.08	0.13	0.05	0.14
Age	0.01	0.01	0.03**	0.01	0.03**	0.01
Sex	-0.10	0.11	-0.05	0.10	-0.07	0.10
LMT (*1998/9*)			0.03***	0.00	0.04***	0.00
Education					0.08	0.06
R^2	0.003		0.216		0.218	
Df	(3, 310)		(4, 309)		(5, 308)	
F	0.73		22.54***		18.41***	
ΔR^2			0.219		0.004	
Df			(1, 309)		(1, 308)	
F			87.34***		1.69	

Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 35. 1998/9 cognitive performance-adjusted regression analysis of 2002/3 Logical Memory Test score residuals in relation to stroke (N=280). Numbers are standardised regression coefficients and standard errors.

Model Term	Model 1		Model 2	
	B	SE	B	SE
Stroke	0.06	0.27	0.04	0.24
Age	0.00	0.01	0.02*	0.01
Sex	-0.00	0.12	0.00	0.10
LMT *(1998/9)*			0.03***	0.00
R^2	0.011		0.185	
Df	(3, 276)		(4, 275)	
F	0.02		16.83***	
ΔR^2			0.196	
Df			(1, 275)	
F			67.23***	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 36. Peak prior cognitive ability-adjusted regression analysis of 2002/3 Logical Memory Test score residuals in relation to stroke (N=199). Numbers are standardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3	
	B	SE	B	SE	B	SE
Stroke	0.46	0.33	0.46	0.33	0.30	0.32
Age	0.00	0.01	0.00	0.01	-0.00	0.01
Sex	-0.02	0.14	-0.02	0.14	-0.01	0.13
NART			0.00	0.00	0.01	0.01
CRP					0.23**	0.07
R^2	0.005		0.008		0.039	
Df	(3, 195)		(4, 194)		(5, 193)	
F	0.70		0.60		2.61*	
ΔR^2			0.001		0.051	
Df			(1, 194)		(1, 193)	
F			0.29		10.55**	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 37. 1998/9 cognitive performance-adjusted regression analysis of 2002/3 Raven's Progressive Matrices score residuals in relation to intermittent claudication (N=211). Numbers are standardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Intermitternt claudication	0.12	0.17	0.20	0.16	0.19	0.17	0.19	0.17	0.20	0.17	0.20	0.17	0.18	0.17	0.19	0.17	0.19	0.17
Age	0.00	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01
Sex	-0.50***	0.13	-0.41**	0.13	-0.42**	0.13	-0.42**	0.13	-0.41**	0.13	-0.41**	0.13	-0.42**	0.13	-0.42**	0.13	-0.43**	0.14
RPM *(1998/9)*			0.04***	0.01	0.04***	0.01	0.04***	0.01	0.04***	0.01	0.04***	0.01	0.04***	0.01	0.04***	0.01	0.04***	0.01
Education					0.03	0.08	---		---		---		0.03	0.08	0.03	0.08	0.03	0.08
Fibrinogen							0.06	0.12	---		---		0.05	0.13	0.07	0.13	0.07	0.13
ICAM-1									0.00	0.00	---		---		0.00	0.01	0.00	0.00
Blood Viscosity											-0.01	0.14	---		---		-0.02	0.14
R^2	0.05		0.149		0.146		0.146		0.145		0.145		0.142		0.138		0.134	
Df	(3, 207)		(4, 206)		(5, 205)		(5, 205)		(5, 205)		(5, 205)		(6, 204)		(7, 203)		(8, 202)	
F	4.78**		10.19***		8.16***		8.17***		8.12***		8.12***		6.80***		5.82***		5.07***	
ΔR^2			0.10		0.001		0.001		0.000		0.000		0.001		0.000		0.000	
Df			(1, 206)		(1, 205)		(1, 205)		(1, 205)		(1, 205)		(1, 204)		(1, 203)		(1, 202)	
F			24.80***		0.17		0.22		0.02		0.00		0.19		0.09		0.01	

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15). *P<0.05; **P<0.01; ***P<0.001.

TABLE 38. 1998/9 cognitive performance-adjusted regression analysis of 2002/3 Raven's Progressive Matrices score residuals in relation to MI (N=315). Numbers are standardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**	
	B	SE	B	SE
MI	-0.13	0.15	-0.04	0.14
Age	-0.00	0.01	0.02	0.01
Sex	-0.46***	0.11	-0.32**	0.10
RPM *(1998/9)*			0.04***	0.01
R^2	0.045		0.161	
Df	(3, 311)		(4, 310)	
F	5.96**		16.07***	
ΔR^2			0.117	
Df			(1, 310)	
F			43.94***	

Myocardial infarction (n=50) includes subjects with MI only (n=12), MI and angina (n=21), MI and intermittent claudication (n=2), MI, angina, and IC (n=15).

*P<0.05; **P<0.01; ***P<0.001.

TABLE 39. Peak prior cognitive ability-adjusted regression analysis of 2002/3 Verbal Fluency Test score residuals in relation to stroke (N=282). Figures shown are standardised regression coefficients and standard errors.

Model Term	Model 1		Model 2	
	B	SE	B	SE
Stroke	-0.31	0.27	-0.32	0.27
Age	-0.02*	0.01	0.02*	0.01
Sex	0.03	0.12	0.04	0.12
NART			0.02*	0.01
R^2	0.007		0.027	
Df	(3, 278)		(4, 277)	
F	1.68		2.97*	
ΔR^2			0.023	
Df			(1, 277)	
F			6.75*	

Stroke (n=17) includes subjects with stroke only (n=11), stroke and angina (n=3), stroke and intermittent claudication (n=3). *P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 40. Peak prior cognitive ability-adjusted regression analysis of 2002/3 Digit Symbol Test score residuals in relation to any CVD (N=254). Numbers are standardised regression coefficients and standard errors.

Model Term	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9		Model 10	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Any CVD	-0.13	0.13	-0.20	0.12	-0.19	0.13	-0.18	0.13	-0.17	0.12	-0.16	0.13	-0.18	0.13	-0.16	0.13	-0.19	0.12	-0.18	0.12
Age	-0.06***	0.01	-0.05***	0.01	-0.05***	0.01	-0.05***	0.01	-0.05***	0.01	-0.04**	0.01	-0.05***	0.01	-0.05***	0.01	-0.05***	0.01	-0.05***	0.01
Sex	0.39**	0.12	0.41**	0.12	0.41**	0.01	0.41**	0.12	0.33**	0.12	0.44***	0.12	0.40**	0.12	0.39**	0.12	0.32*	0.13	0.35**	0.12
NART			-0.03***	0.01	-0.03***	0.01	-0.03***	0.01	-0.02***	0.01	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01
Anxiety Score (*N+1 Log transformed*)					-0.05	0.22	---		---		---		---		---		---		---	
Depression Score (*N+1 log transformed*)							-0.14	0.26	---		---		---		---		---		---	
Pack-Year (*Square root transformed*)									-0.07**	0.02	---		---		---		---		---	
Systolic Pressure											-0.00	0.00	---		---		---		---	
Diastolic Pressure													-0.01	0.00	---		---		---	
Interleukin-6 (*Log transformed*)															-0.18	0.11	---		---	
Haematocrit																	-0.03	0.20	---	
Blood Viscosity																			-0.22	0.12
R^2	0.107		0.156		0.153		0.154		0.184		0.163		0.159		0.162		0.162		0.164	
Df	(3, 250)		(4, 249)		(5, 248)		(5, 248)		(5, 248)		(5, 248)		(5, 248)		(5, 248)		(5, 248)		(5, 248)	
F	11.11***		12.69***		10.12***		10.18***		12.40***		10.86***		10.57***		10.79***		10.76***		10.94***	
ΔR^2			0.052		0.000		0.001		0.031		0.010		0.006		0.009		0.009		0.011	
Df			(1, 249)		(1, 248)		(1, 248)		(1, 248)		(1, 248)		(1, 248)		(1, 248)		(1, 248)		(1, 248)	
F			15.49***		0.05		0.31		9.54**		3.13		1.93		2.84		2.71		3.45	

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17). *P<0.05; **P<0.01; ***P<0.001. NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 40 (cont.)

Model Term	Model 11		Model 12		Model 13		Model 14		Model 15		Model 16		Model 17	
	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE	B	SE
Any CVD	-0.18	0.13	-0.16	0.12	-0.12	0.13	-0.12	0.13	-0.10	0.13	-0.10	0.13	-0.10	0.13
Age	-0.05***	0.01	-0.05***	0.01	-0.04**	0.01	-0.04**	0.01	-0.04**	0.01	-0.04**	0.01	-0.04**	0.01
Sex	0.41**	0.12	0.33**	0.12	0.36**	0.12	0.35**	0.12	0.34**	0.12	0.31*	0.13	0.31*	0.13
NART	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01	-0.03***	0.01
Anxiety Score (*N+1 Log transformed*)	0.00	0.24	0.07	0.24	0.05	0.24	0.05	0.24	0.02	0.24	0.02	0.24	0.01	0.24
Depression Score (*N+1 log transformed*)	-0.15	0.28	-0.09	0.28	-0.15	0.28	-0.14	0.28	-0.10	0.28	-0.09	0.28	-0.08	0.29
Pack-Year (*Square root transformed*)			-0.07**	0.02	-0.07**	0.02	-0.07**	0.02	-0.07**	0.02	-0.06**	0.02	-0.06**	0.02
Systolic Pressure					-0.00	0.00	-0.00	0.00	-0.00	0.00	-0.00	0.00	-0.00	0.00
Diastolic Pressure							-0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.01
Interleukin-6 (*Log transformed*)									-0.13	0.11	-0.11	0.11	-0.10	0.11
Haematocrit											-0.01	0.02	-0.01	0.02
Blood Viscosity													-0.08	0.16
R^2	0.150		0.178		0.186		0.183		0.184		0.182		0.180	
Df	(6, 247)		(7, 246)		(8, 245)		(9, 244)		(10, 243)	(11, 242)	(12, 241)			
F	8.45***		8.81***		8.23***		7.29***		6.70***		6.13***		5.63***	
ΔR^2	0.001		0.030		0.011		0.000		0.004		0.002		0.001	
Df	(1, 247)		(1, 246)		(1, 245)		(1, 244)		(1, 243)		(1, 242)		(1, 241)	
F	0.27		9.29**		3.53		0.02		1.33		0.54		0.29	

Any CVD (n=149) excludes subjects with prevalent or incident stroke (n=17). *P<0.05; **P<0.01; ***P<0.001. NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 41. Peak prior cognitive ability-adjusted regression analysis of 2002/3 Digit Symbol Test score residuals in relation to intermittent claudication (N=221). Numbers are standardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**		**Model 3**	
	B	SE	B	SE	B	SE
Intermittent claudication	-0.09	0.17	-0.21	0.17	-0.21	0.18
Age	-0.04**	0.01	-0.04**	0.01	-0.04**	0.01
Sex	0.36**	0.13	0.40**	0.12	0.40**	0.13
NART			-0.03***	0.01	-0.03***	0.01
Interleukin-6 *(Log transformed)*					0.00	0.12
R^2		0.07		0.143		0.139
Df		(3, 217)		(4, 216)		(5, 215)
F		6.62***		10.14***		8.08***
ΔR^2				0.074		0.000
Df				(1, 216)		(1, 215)
F				19.06***		0.00

Intermittent claudication (n=57) includes subjects with intermittent claudication only (n=26), intermittent claudication and angina (n=14), MI and intermittent claudication (n=2), MI, angina, and intermittent claudication (n=15). *P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

TABLE 42. Peak prior cognitive ability-adjusted regression analysis of 2002/3 Digit Symbol Test score residuals in relation to stroke (N=236). Numbers are standardised regression coefficients and standard errors.

Model Term	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
	B	SE	B	SE	B	SE	B	SE	B	SE
Stroke	0.09	0.35	0.13	0.34	0.27	0.34	0.23	0.35	0.33	0.34
Age	-0.04**	0.01	-0.04**	0.01	-0.04**	0.01	-0.04**	0.01	-0.04**	0.01
Sex	0.40**	0.13	0.39**	0.12	0.31*	0.12	0.33**	0.13	0.28*	0.13
NART			-0.02**	0.01	-0.02***	0.01	-0.02***	0.01	-0.02**	0.01
Pack-Year *(Square root transformed)*					-0.07**	0.02	---		-0.06*	0.03
Blood Viscosity							-0.19	0.13	-0.15	0.13
R^2	0.070		0.109		0.133		0.114		0.134	
Df	(3, 232)		(4, 231)		(5, 230)		(5, 230)		(6, 229)	
F	6.89***		8.18***		8.22***		7.04***		7.09***	
ΔR^2			0.042		0.027		0.009		0.005	
Df			(1, 231)		(1, 230)		(1, 230)		(1, 229)	
F			11.15**		7.45**		2.30		1.37	

*P<0.05; **P<0.01; ***P<0.001.

NART=National Adult Reading Test (an estimate of peak prior cognitive ability).

CHAPTER SIX

Discussion

6.1. INTRODUCTION

In this chapter the findings from the study are discussed. First, the results from the analyses of the relationship between cognitive test performance and CVD status are examined according to vascular morbidity type. Then, the associations between vascular risk factors and neuropsychological functioning are considered. Both sets of findings are examined in relation to results from published studies. General aspects of the study's methodological and analytical approaches are also discussed. Finally, the chapter concludes with an examination of the potential neuropathological mechanisms underlying vascular cognitive decline.

6.2. SUMMARY OF MAIN FINDINGS

Cardiovascular diseases constitute a major determinant of morbidity and mortality in the adult population. The present study further demonstrated that vascular disease is associated with a progressively steeper decline in neuropsychological functioning in older people. Specifically, subjects with stroke performed worse on a majority of cognitive tests compared to those without major clinical CVD. In multiple linear regression analyses, stroke was associated with a significantly greater decline in general cognitive function (the proportion of the total variance accounted by stroke ranged from 0.32 to 1.25%) as well as in verbal memory (stroke explained 1.21% of the total variance) and word fluency (1.80% of the total variance was attributed to stroke), independent of prior cognitive ability and demographic and vascular risk factors.

Relative to subjects without symptomatic CVDs, there was evidence of worse general cognitive function and lower scores on most mental tests in those with demonstrable vascular disease other than clinical stroke. In particular, participants with MI but without a diagnosed stroke scored lower on most cognitive measures, although only significantly so on tests of verbal memory and non-verbal reasoning. In multiple linear regression analyses, MI predicted greater decline in non-verbal reasoning (0.90% of the total variance was attributed to MI) after adjustment for possible confounding factors. In contrast, the study did not support an independent association between angina pectoris and cognitive decline in elderly people.

The study further demonstrated worse performance on most cognitive tests in participants with symptomatic PAD compared to subjects without major clinical CVD. Multiple linear regression analyses showed PAD was notably associated with a significantly greater decline in general cognitive function (accounting for 0.29% of the total variance) as well as in verbal memory (0.88% of the total variance was attributed to PAD) after possible confounding by demographic and vascular risk factors was taken into account.

In a number of multivariate models, several potentially modifiable CVD risk factors had measurable negative effects on cognitive function. Specifically, baseline diastolic blood pressure predicted decline in verbal memory (0.61% in the total variance was explained by blood pressure) and body mass index was negatively associated with general cognitive decline (BMI accounted for 0.28% of the total variance in general function). Both smoking and blood viscosity were also associated with an increased decline in information processing speed (about 1.46% and 4.0% of the total variance were explained by these, respectively), and in addition, blood viscosity predicted steeper decline in general cognitive function (1.32% of the total variance was accounted for by blood viscosity). Of the inflammatory and haemostatic markers assessed in the study, IL-6 in particular was related to a significantly steeper decline in information processing speed (IL-6 was related to between 1.85 and 2.16% of the total variance). In contrast, level of formal education was inversely associated with decline in verbal memory (education accounted for between 0.92 and 2.04% of the total variance), independently of prior cognitive ability, demographic factors and vascular disease.

Further analyses of the data were performed where the associations of vascular risk factors and diseases with change in individual mental tests were examined after the simultaneous control for performance on the general cognitive factor. These analyses revealed that the above relationships were largely explained by the relationship of vascular disease and risk factors with general mental ability rather than with individual functions per se.

6.3. CARDIOVASCULAR DISEASES AND COGNITIVE DECLINE

6.3.1. Stroke

Any meaningful comparison of the present findings with published results is challenging given the methodological heterogeneity (e.g. regarding the selection of the population under study, the comparison group used, the choice of cognitive measures, the approach to the control for potential confounding, data analysis etc.) between studies. Also, as yet, few previous population studies have comprehensively assessed longitudinal change across major cognitive domains in relation to stroke. In the light of our approach to the examination of the association between stroke and cognitive function, the present study is likely to add to the existing research base in several different ways. For example, in the context of research of the impact of stroke on general cognitive function, we employed a novel approach for assessing general mental ability which is in line with current theoretical notions of the hierarchical structure of human cognitive abilities (Carroll, 1993; Deary and Batty, in press).

In contrast, the majority of previous studies have solely administered the MMSE for assessing general mental ability in community samples but a single global measure may be ill-suited for this purpose (Morris et al., 1999). Regarding the current context, its validity in the study of cognitive function among subjects with stroke has also been questioned (de Koning et al., 1998). As a summary measure of general cognitive function, there is great potential for ceiling effects with respect to performance on the MMSE in non-demented samples. Moreover, an important limitation of the MMSE stems from its relative insensitivity to such subtle changes in cognitive function which might be expected in studies of cognitively-intact elderly people. In such circumstances, the use of the MMSE may result in an underestimation of the true extent of cognitive decline.

Similar to the above, we demonstrated that stroke, as a clinical entity, was significantly related to worse general cognitive factor scores, representing the variance common to the specific mental tests we used, when the performance of people with stroke and non-vascular controls was compared (see tables 12 and 19). Upon the investigation of individual change in general ability, stroke significantly predicted steeper cognitive decline (see tables 14 and 20). Despite differences in measures of general ability, our findings converge with those of previous population studies where stroke has been associated with a worse cognitive outcome.

For example, in a considerably larger sample than ours, Zhu et al. (1998) reported that Swedish stroke survivors aged 75 years and older were significantly more likely to score below 24 on the MMSE. However, the analysis was cross-sectional and change in MMSE performance over time was not assessed in relation to stroke status. On the other hand, in the Zutphen Elderly Study, stroke was related to more than a four-fold increased risk of three-year global cognitive decline (defined as a change of at least two points on the MMSE) although, in contrast to the present study, the findings were based on males (Kalmijn et al., 1996). Also, in the Framingham study, stroke was linked to a subtly increased decline in mean MMSE performance over a short period of only six months in elderly subjects (Kase et al., 1998). Similarly, Haan et al. (1999) associated stroke with a steeper decline in performance on the modified MMSE scale over a seven-year follow-up in the Cardiovascular Health Study. Despite the length of the follow-up in this study which was substantially greater than that available to us for the measurement of actual change in general ability, the level of decline was only modest and unlikely to be of clinical significance.

In contrast to the above, our results deviate from those reported by Srikanth et al. (2003) who failed to find a significant difference in mean MMSE scores when subjects with stroke and 99 age and sex-matched non-stroke controls were cross-sectionally compared. Although the discrepancy between this and the present study might in part be attributed to differences in measures of general cognitive ability, it is also possible that the lack of difference between people with stroke and controls observed by Srikanth et al. (2003) might have been caused by the recruitment of control subjects who in fact did not differ from those with stroke regarding the extent of non-stroke vascular disease and atherosclerotic risk factors such as diabetes and hyperlipidaemia. Similarly, stroke was not associated with a significantly steeper three-year decline in mean performance on the MMSE in the Longitudinal Aging Study Amsterdam (Dik et al., 2000). However, relative to non-stroke elderly, diseased subjects did demonstrate a greater change in global scores over the follow-up. Therefore, the lack of statistical significance might have been the result of inadequate statistical power to detect modest MMSE-based changes in general cognition over a relatively short follow-up.

With respect to specific indices of cognitive function, our age and sex-adjusted comparison of people with stroke and non-vascular subjects pointed to a significantly worse performance by those with stroke on several tests, including those assessing verbal memory, verbal fluency and information processing speed (see tables 12 and 19). Upon further adjustment for baseline test performance, those with stroke only differed from healthy subjects in mean verbal memory performance. After similar control for performance on the NART, the diseased subjects performed significantly worse on average on verbal memory, verbal fluency and information processing speed tasks. Furthermore, we also demonstrated that stroke was independently associated with an increased four-year decline in verbal memory (see table 24). And when estimated from a pre-morbid level of cognitive function, stroke also predicted a greater decline in verbal fluency (see table 28). Although Srikanth et al. (2003) failed to find statistically significant differences between people with and without stroke in mean cognitive test scores, the stroke group did perform less well on several tests, including measures of information processing speed and components of verbal memory. More specifically, subjects with stroke had slightly lower delayed verbal memory scores compared to stroke-free controls but no differences were found regarding immediate recall. It is unlikely that the differences in results between this and the present study can entirely be attributed to the use of different memory tasks. For example, in the present study verbal memory was assessed using immediate and delayed recall of two stories (WMS-R Logical Memory Test) whereas Srikanth et al. (2003) administered the Rey Auditory Verbal Learning Test, which is based on recalling a list of 15 words. Although it is conceivable that recalling a list of random words (free recall) might pose different challenges for memory functioning than memorising a story (which may contain some cues facilitating recall), the significantly worse verbal memory performance among people with stroke in the present investigation may also to some extent be explained by the use in the current study of control subjects without any major vascular pathology rather than simply free of clinical stroke.

In a similar research context, Dik et al. (2000) demonstrated an improvement during follow-up in mean performance on both the immediate and delayed components of the Rey Auditory Verbal Learning Test among people with and without stroke, although to a slightly lesser degree in delayed functioning among the former group. To the extent which practice effects affected the findings of the present study, particularly the four-year change in verbal memory performance, the associations reported herein are likely to be an underestimation of the true level of change seen among both diseased and non-diseased participants. Such effects would, however, not have affected the individual differences in memory change over time which, in contrast to both the above studies, we examined as well.

The results of the present study are in further contrast with that of Srikanth et al. (2003) who found no differences between subjects with stroke and controls with respect to verbal fluency performance. It is possible that the short word-producing task (Controlled Oral Word Association Test) used by Srikanth et al. (2003) simply was not sensitive enough to separate between diseased and non-stroke subjects with respect to potential deficits in frontal lobe executive functioning. Although similar speculations are likely to apply to the present study given the similarities of the tasks used in these two investigations, our findings of a relatively greater verbal fluency dysfunction among those with stroke are also likely to have been influenced by our selection of relatively less morbid control subjects than in the above study. However, it is likely that future population studies examining stroke and cognitive function need to comprehensively probe this cognitive domain through the administration of multiple executive functioning tests.

In another set of analyses, stroke did not significantly predict decline in information processing speed when estimated over the life-span. With respect to this cognitive domain, the null-finding contradicts the results of Haan et al. (1999) who associated baseline stroke with a modest but statistically significantly greater decline in information processing speed over a follow-up of seven years. Further to the fact that both studies assessed information processing speed from performance on the Digit Symbol Test, one might have expected a significant relation between stroke and processing speed in the present context given our attempt to model this relationship over an effectively much longer period of cognitive change (i.e. from 'best-ever' level) compared to that available to Haan and colleagues (1999). Indeed, the negative coefficient for stroke in our regression model suggested a steeper decline in relation to stroke although we were unable to demonstrate this statistically.

Whereas almost by definition stroke denotes a direct impact on the underlying neural substrate, we demonstrated through a further novel analysis of the data that the associations of stroke with decline in particular mental functions were largely attributed to the relation of stroke with general cognitive ability rather than the elements of the individual measures per se (although not shown here, preliminary analyses demonstrated no significant differences in physical impairment between people with and without stroke although in some instances individuals who had had stroke clearly showed some sensorimotor difficulties which could have affected their performance on the DST but, on the whole, these were unlikely to account for the associations reported here). As discussed in detail in a later section, it is possible that acute ischaemia may lead to disruption of complex, intricate neural networks underlying general cognition by affecting the functional connectivity of diverse cerebral regions (Duncan et al., 2000; Newman and Just, 2005). Similarly or in conjunction with the above, ischaemic alterations disrupting the structural integrity of subcortical white matter tracts, essential to intact inter-regional communication of cortical and subcortical grey matter areas, may affect not only the functional capacity of the white matter but also the processing ability of neurocognitive networks (Newman and Just, 2005).

Although our cut-off point for the diagnosis of stroke was approximately six months prior to follow-up cognitive testing, for the majority of subjects, the ischaemic event had been diagnosed prior to the baseline cognitive assessment. After the exclusion of people with stroke occurring during cognitive follow-up, none of the associations reported earlier with decline in cognitive performance over the four-year study interval changed direction even though some became attenuated and no longer remained statistically significant. Thus, whereas people with stroke no longer remained significantly more impaired in general cognitive ability when compared to non-vascular controls, their average performance on verbal memory was still significantly lower. Similarly, stroke continued to exert independent negative effects on both general ability and verbal memory after our examination of the four-year individual change in these cognitive functions.

A number of factors may act as possible confounders of the association between stroke and cognitive decline which, if not adequately controlled, may give rise to spurious results. In the present study, an effort was made to control for potential confounding by prior cognitive ability further to any confounding arising from differences in demographic composition between subjects with stroke and controls. Although our approach is in line with that of some previous population studies (e.g. Dik et al., 2000; Kalmijn et al., 1996) others have only taken into account differences in education or social status between those with stroke and healthy groups (Haan et al., 1999; Srikanth et al., 2003; Zhu et al., 1998). However, given the wide variation of ability levels within the same education or social class level, these factors are unlikely to fully control for subjects' prior level of mental ability. As a result, residual confounding by prior cognitive ability may be difficult to rule out as an alternative explanation for these findings.

In further contrast to most previous research, the present results are unlikely to be explained away by confounding by differences in either levels of mood or conventional and novel atherosclerotic risk factors. For example, we found that subjects with stroke had elevated HADS-determined levels of anxiety compared to the non-vascular controls but changes in mood may negatively affect cognitive test performance (Morris et al., 1999). The stroke subjects also had significantly higher rates of smoking and greater values of systolic blood pressure, serum CRP, and whole blood viscosity. Each of these may be independently associated with cognitive outcomes. In this regard, only Zhu et al. (1998) demonstrated a greater risk of general cognitive impairment in subjects with stroke after controlling for SBP and ICD-classified CHD. Therefore, our findings suggest that the progressive decline in cognitive function observed in people with stroke may in fact depend on those mechanisms resulting in acute cerebral ischaemia rather than on any concomitant influences of atherosclerotic risk factors. Possibly, the continuing advancement of large-vessel vascular pathology might induce progressively more hypoperfusion-related injury to deeply-located cerebral areas (de la Torre, 2006). Also, progressive cognitive decline in the absence of further clinical events might be attributed to the cumulative impact of continuous, multiple, asymptomatic, cerebral microemboli arising from extra –or intracranial atheromatous lesions (Russell, 2002). The fact that the association between stroke and decline in specific cognitive tests was totally mediated by the effects of stroke on the general cognitive factor might imply that those neurocognitive processes represented by general ability would be particularly vulnerable to any such vascular pathology.

In addition to the above, our findings are unlikely to be the result of stroke-induced neurological deficits, including aphasic disabilities. Although mild disability affecting some participants with stroke may not be excluded, the inclusion of severely impaired subjects was improbable given these would not have been forwarded by the GPs. Also, a signed informed consent was required from all participants who subsequently were probed for any sensory-motor difficulties.

The present findings are based on study participants who at any point throughout follow-up were found to meet pre-determined criteria for the diagnosis of stroke. The comprehensive approach employed by the EAS for the detection of clinical stroke is likely to have minimised the likelihood of inclusion of false-negatives cases. However, given the use of different diagnostic criteria at different points in the study, there might be potential for misclassification under certain circumstances. For example, where the diagnosis was solely based on clinical symptoms (but computerised tomography was not carried out or initial scan showed negative findings and no follow-up scan performed) or on subject's recall of a doctor's diagnosis of stroke, some subjects who did not have true acute cerebrovascular disease despite symptoms might have been falsely identified as cases. On the other hand, it is also possible that some persons falsely recalled having ever been told by a doctor that they had suffered a stroke. In any case, any misclassification whereby a truly healthy individual had been categorised as having stroke would have lowered the overall morbidity level of the stroke group. As a result, such a bias would resulted in the findings reported here being an underestimation of the true extent of stroke-induced cognitive deterioration.

Also, due to the lack of systematic scanning of participants with stroke, information on the various pathological aspects of the event, including aetiological type, lesion site, and severity were not available to us. However, on the basis of published data, it is likely that the majority of subjects with stroke in our study had suffered a thromboembolic infarct (Merino and Hachinski, 2001). In addition, since stroke severity is strongly related to early mortality and non-participation (Srikanth et al., 2003), the current sample is likely to comprise survivors with mild to moderate stroke pathology. The fact that we employed an interval of six months between the diagnosis of stroke and follow-up cognitive testing may further have reduced the possibility of people with severe stroke being included in the study.

In line with most previous studies, we did not have brain scan data on subjects comprising our comparison group. Therefore, we can only speculate whether any might have had clinically unrecognised cerebral lesions. Such silent infarcts would have increased the morbidity level of the comparison group and further attenuated any differences between these and the stroke group. Most previous reports have compared the cognitive performance of people with stroke with that of non-stroke controls, although on some occasions the controls have had a similar non-stroke vascular burden as the disease group.

Evidence shows non-symptomatic cerebral infarcts may be a common finding in non-stroke vascular patients (Pardo et al., 1998) and these may be negatively associated with performance on cognitive tests, as will be discussed later. As mentioned earlier, it is possible that the use of relatively morbid controls may have contributed to the lack of significant findings reported in some studies. In contrast, our comparison group comprised subjects without prospectively-determined clinical CVD. Although we cannot rule out the possibility of sub-clinical atherosclerotic pathology among some non-vascular controls, our comparison group is likely to be both physically and cognitively healthier than those used in most previous investigations.

6.3.2. Coronary Heart Disease

Cognitive function has been a relatively understudied outcome in population-based epidemiological investigations of non-stroke vascular diseases. In the present study, the focus was on the investigation of patterns of cognitive decline in both general ability and specific functions in relation to two major CHD syndromes: angina pectoris and MI.

With respect to general cognitive ability, as indexed in the current study by a general factor computed from subjecting individual mental tests to a principal components analysis, significant associations with MI were found in age and sex-adjusted comparisons with subjects without major clinical CVD (see tables 11 and 18). After further control for prior cognitive ability, people with MI continued to demonstrate lower yet non-significant mean general ability scores. On the other hand, angina was not associated with general cognitive function in any of the analyses performed (see tables 9 and 16). Despite differences in measures of general cognition across investigations, our findings are in line with results from some but not all previous population studies which have examined cognitive outcomes in relation to these CHD syndromes separately. Thus, although using a somewhat larger sample than available for the present analysis, Tilvis et al. (2003) failed to find significant differences in average performance on the MMSE in a cross-sectional comparison of elderly subjects with and without history of MI. Identical null-findings came from a very large cohort based on Japanese-American men, despite MI subjects with a history of stroke were not excluded from the analysis (Petrovitch et al., 1998). In yet another set of cross-sectional data, which also was restricted to elderly males, Elwood et al. (2002) failed to associate prevalent MI with greater global cognitive dysfunction when patients' test performance was compared to that of subjects without any evidence of clinical vascular disease. In addition, although few studies have examined longitudinal change in general cognitive function in relation to specific coronary syndromes, most have failed in their attempt to demonstrate a significant association between the presence of symptomatic CHD in older people and MMSE-based global cognitive decline (e.g. Eslinger et al., 2003; Piguet et al., 2003; Zhu et al., 1998).

On the other hand, the fact that we did not find a significant relation of either CHD syndrome with general ability is partly in conflict with other published evidence, including that by Breteler et al. (1994) who demonstrated an overall shift in the distribution of MMSE scores in relation to MI in an early cross-sectional analysis based on the Rotterdam Study cohort. Whereas significance testing was not performed on the data, the actual mean difference in MMSE scores between subjects with and without MI was only modest after correction for variation in age and level of education. Although differences regarding how general ability was measured in the two studies need to be borne in mind, on their own these may not fully account for the discrepancy in findings. Indeed, whereas in the present study MI was associated with significantly worse general cognitive function (the difference between patients and healthy subjects amounted to approximately a third of a standard deviation), the relationship did not hold after controlling for differences in prior ability between cases and controls. Adjustment for differences regarding level of education in the Rotterdam Study might not have provided adequate control for prior ability differences between diseased and non-diseased subjects, given the potentially wide range of cognitive ability levels among individuals within the same education category. As a result, some residual confounding by prior ability cannot be ruled out in the data by Breteler et al. (1994). In addition, other differences between the two studies might also have played a role, such as the fact that the diagnosis of MI in the Rotterdam Study was solely based on ECG changes whereas most events in the current analysis were diagnosed on the basis of presenting chest pain and elevated cardiac enzymes. In this regard, the clinical features of MI in the Rotterdam Study might be indicative of more severe coronary disease than that experienced by the majority of cases in the current study. On the whole, however, our inability to demonstrate significant differences in general ability between those with MI and non-vascular controls needs to be viewed in the light of the relatively conservative approach chosen for controlling for potential confounding.

In a similar manner, the absence of an association with angina in the current study contradicts findings from the Caerphilly study where elderly males with angina scored significantly worse on two measures of global mental ability (Elwood et al., 2002). Although the two studies differed with respect to type of measurement of general cognition, both administered a symptom-based questionnaire for the assessment of angina. However, it is unclear whether the disease group used in the Caerphilly study was mutually exclusive of other manifestations of CVD. On the other hand, given that we kept the angina category distinct of more severe vascular morbidity in order to study cognitive function in relation to a relatively mild, non-acute form of atherosclerotic vascular disease, the observed discrepancies in findings might partly be attributed to differences regarding the vascular burden among subjects comprising the exposure group.

Of the individual cognitive measures that were administered, diseased subjects scored on average lower on tests of verbal memory, non-verbal cognitive ability, and information processing speed relative to non-vascular subjects (see tables 11 and 18). After adjustment for demographic factors and prior cognitive ability, diseased and healthy subjects differed significantly in mean performance on tests of both verbal memory and non-verbal intelligence. No significant associations were found with angina. Our findings are similar in part to those of Elwood et al. (2002) who in an earlier analysis had reported significantly worse performance on a combined task of verbal and non-verbal reasoning in elderly subjects with MI. However, the administration of a more comprehensive battery of mental tests in the current study allowed the examination of major cognitive domains, including aspects of memory, in relation to coronary disease. Our results are also in line with those reported by Singh-Manoux et al. (2003) who noted that subjects with MI scored modestly yet significantly lower on average on half of the tests that were administered (verbal reasoning, general knowledge, and semantic fluency). Despite differences in measures of cognitive function and sample structure, both our findings and those by Singh-Manoux et al. (2003) suggest that MI may be associated with deficits in a relatively restricted set of cognitive functions, compared to that seen for either stroke or PAD. Importantly, whereas neither of the above studies examined individual change in cognitive performance in relation to coronary disease, we further demonstrated that MI independently predicted a progressively steeper decline in non-verbal reasoning over the four-year cognitive follow-up (see table 27).

The absence of a relationship between angina and domain-specific test performance in the current study is in conflict with findings from the Caerphilly study where significant differences in verbal and non-verbal reasoning were found when subjects with angina and non-vascular controls were compared (Elwood et al., 2002). Although difficult to ascertain, this discrepancy could have arisen from the emphasis we placed on using a relatively homogeneous, mutually exclusive disease category, as discussed previously in the text. Similarly, the inclusion of angina subjects with other concomitant vascular morbidity might also have contributed to the positive findings reported by Singh-Manoux et al. (2003) who demonstrated significantly lower mean scores in participants with angina on tests of verbal memory, verbal and non-verbal reasoning, knowledge, and verbal fluency.

A major limitation of previous studies examining the relationship of CHD with cognitive outcomes has been the inadequate control of potential confounding factors. Specifically, in few of the above analyses was possible confounding by prior cognitive ability sufficiently taken into account. When attempted, however, most studies have either adjusted for highest level of education completed (e.g. Breteler et al., 1994; Petrovitch et al., 1998) or occupational-based socioeconomic status (e.g. Elwood et al., 2002; Singh-Manoux et al., 2003). As discussed already, statistical adjustment for differences in these characteristics may not provide a full control for any confounding assigned to prior cognitive ability. In contrast, our findings were unlikely to be explained away by differences between diseased and non-diseased subjects in prior ability.

The availability of data on several conventional and novel vascular risk factors further allowed us to examine whether the association between CHD and cognitive function existed independently of these parameters. In particular, subjects with MI had significantly lower pre-morbid cognitive ability levels, were less formally educated, and of lower social standing than the non-vascular controls. Also, both anxiety and depression levels were significantly elevated in subjects with MI. Moreover, these subjects also had greater smoking rates as well as higher levels of BMI, blood pressure, IL-6, and blood viscosity. In contrast, those with MI had significantly lower HDL cholesterol levels compared to subjects without any vascular diseases. As a result, the fact that we found an independent relationship between MI and progressive decline in non-verbal reasoning skills suggests that, at least to a degree, the association may actually depend on the underlying vascular pathological processes and their continuing development. In this respect, CHD and cognitive dysfunction may both be manifestations of systemic atherosclerosis. Indeed, the diffuse nature of atherosclerosis is well recognised and both significant intra -and extracranial disease may increase the risk of clinically silent cerebral infarcts and other vascular-related cerebral pathology (Drouet et al., 2002; Mosley et al., 2005). However, it has been pointed out that MI per se does not adequately represent the level of systemic atherosclerosis in the body which possibly is reflected in the generally weaker and more restricted cognitive effects found in such patients relative to those with other CVD manifestations (Singh-Manoux et al., 2003). Therefore, on-going clinically unrecognised, cardiogenic brain embolism, rather than silent infarcts arising from an in situ thrombosis of either cerebral or other extracranial arteries, might be an important vascular mechanism associated with progressive cognitive decline in MI patients (Vingerhoets, 2001). Indeed, it has been pointed out that as many as 15-30% of all ischaemic strokes may be cardiogenic in origin (Boden-Albala and Sacco, 2004). Similarly, it is also possible that, in some patients with MI, reduced cardiac output in relation to chronic ischaemic cardiac failure may lead to decreased cerebral perfusion and either recurrent or continuous episodes of hypoxia (Vingerhoets, 2001). Given that the relationship between MI and decline in performance on individual cognitive tests was fully mediated by the effects of MI on the general cognitive factor, these findings underscore the particular vulnerability of the neuropsychological processes underlying general cognitive ability in older subjects with ischaemic cardiac disease.

In the present study, diagnosis of angina was predominantly based on information collected using the WHO Questionnaire. Although this questionnaire is both a widely used and valid tool for classifying individuals with symptoms and signs of transient cardiac ischaemia, there is evidence suggesting it may have low overall specificity, and particularly so in women (Bowling, 1995). However, to the extent that our angina category included false positive cases, any misclassification of cases would have lowered the overall vascular morbidity level of our exposure group. Therefore, further to the fact that our angina category was kept mutually exclusive of other clinical CVD, our null-findings suggest that cognitive function may be relatively preserved in the context of relatively mild, non-acute coronary disease.

Because of the proportionately few subjects diagnosed solely as having MI, we were unable to preserve the mutual exclusiveness of the MI morbidity category. More specifically, more than half of the MI subjects had also met study criteria for either angina or lower-extremity arterial disease, or both (but not clinical stroke). Although not ideal, few previous studies have investigated cognitive outcomes in relation to a mutually exclusive MI category. However, in contrast to earlier studies, our use of broad criteria for the diagnosis of MI may have facilitated the inclusion of participants with relatively mild to moderate myocardial ischaemia in the study. For example, as mentioned briefly before, most events in the present study were diagnosed during follow-up on the basis of chest symptoms and elevated enzyme levels. In contrast, only a minority demonstrated diagnostic ECG alterations further to clinical signs. Whether these patterns may partly be reflecting better survival chances of patients with mild to moderately severe MI is difficult to ascertain. However, we also included cases who did not meet diagnostic criteria for a definite ischaemic event, although these have been deliberately excluded in other investigations. Collectively, it is likely then that, in comparison to most published results, our findings are based on the cognitive experience of relatively less morbid survivors of myocardial ischaemia.

6.3.3. Peripheral Arterial Disease

The present analysis further adds to the relatively limited population-based literature on cognitive function in elderly persons with symptomatic lower-extremity arterial disease. Our results revealed significant differences between participants with intermittent claudication and non-vascular controls in general cognitive function, with the former showing greater deficits after adjustment for demographic factors and prior mental ability (see tables 10 and 17). In addition, we further demonstrated that symptomatic PAD was associated with a significantly accelerated decline in general ability over the four-year cognitive follow-up (see table 13). Despite methodological differences between studies, such as regarding the approach to assessment of general cognitive function and the analysis of the association under study, on the whole, our findings point to the direction of those reported by some although not all earlier investigations. For example, Tilvis et al. (2004) found a significant cross-sectional association between the presence of intermittent claudication at baseline and mean performance on the MMSE in elderly participants in the Helsinki Aging Study. Moreover, claudication was related to an increased risk of decline in global cognitive performance during the first year of cognitive follow-up. Although unclear in the above study, the group of subjects with intermittent claudication in the present analysis was mutually exclusive of clinical stroke. Also, in addition to statistically adjusting for age and sex, we also paid attention to potential confounding by prior cognitive function. Although Tilvis et al. (2004) failed to make similar adjustments in their cross-sectional comparison, differences between cases and non-cases in baseline performance on the MMSE were taken into account in the longitudinal analysis. However, in contrast to the one-year follow-up results, an association between intermittent claudication and five-year cognitive decline was not found, which might have been due to the high selective mortality among cases during follow-up (Tilvis et al., 2004). The discrepancy between our longitudinal findings and these results might be attributed in part to the higher baseline age of the above sample relative to that of our subjects. Indeed, the possibility that Tilvis et al. (2004) examined not only older but relatively more diseased subjects than we did could have contributed to the proportionately high attrition of cases over the follow-up and the simultaneous disappearance of the association with the five-year cognitive decline.

Further to the above, our findings also seem in conflict with results published from two other population studies. In the first, Piguet et al. (2003) did not find any significant differences between very old subjects with and without intermittent claudication at baseline in the level of decline in performance on the MMSE over six years of follow-up. Similar to that described for the study by Tilvis et al. (2004), it is possible that the absence of a relation with intermittent claudication in these data might have been induced by selective attrition of relatively older and more morbid cases during follow-up. Also, it may be that the MMSE proved to be insensitive to perhaps more subtle cognitive decline experienced by relatively milder cases surviving up to follow-up cognitive testing. Furthermore, in the second report, Elwood et al. (2002) failed to detect a significant cross-sectional association between intermittent claudication and performance on two measures of global cognitive function. This was despite the authors compared test scores of cases to those of a group of subjects without evidence of any clinical vascular disease, an approach also undertaken in the present study. However, despite low numbers of diseased subjects, they did perform worse than non-cases on both measures, suggesting that the lack of significant difference might partly have been the result of insufficient statistical power.

In addition to the relationship with general cognitive function, we also found significant age and sex-adjusted differences between diseased and non-vascular controls in the performance on tests of verbal memory, non-verbal reasoning skills and information processing speed (see tables 10 and 17). After further adjustment for prior cognitive ability, either measured at baseline or estimated 'best-ever' level, the differences remained significant. The results from our mean comparison are in line with those described by Singh-Manoux et al. (2003) who found scores on tests of short-term memory, verbal and non-verbal reasoning, word recognition and knowledge and executive functioning modestly but significantly lower in male claudicants compared to non-vascular controls. Similar patterns were seen in female patients with the exception of deficits in memory and aspects of executive function. Also, although Elwood et al. (2002) failed to show a significant association of claudication with performance on tests of verbal and non-verbal reasoning and slower mental speed, the cases who were few in number actually did obtain lower mean scores on all the measures. From the point of view that we found a relationship with PAD using a different battery of cognitive measures to that administered in the above studies, our findings lend additional weight to the existence of a relationship between chronic vascular disease and cognitive deficits in adults. However, in further contrast to the above studies, we demonstrated through an analysis of individual change in cognitive performance that intermittent claudication was also associated with an increased decline in verbal memory over the four-year study interval (see table 22).

Previous studies have documented high levels of diverse potentially modifiable vascular risk factors in patients with symptomatic arterial leg disease (Hooi et al., 1998). In our comparison of subjects with intermittent claudication and non-vascular controls, several significant differences emerged with respect to levels of particular vascular risk factors. As an example, the diseased subjects in our study were more likely to show signs of anxiety and depression at the time of cognitive testing in 2002/3 and have ever smoked when interviewed at baseline in 1987/8. In addition, they reported having completed a lower level of formal education. Importantly, the claudication group also had significantly raised levels of various physiological variables, including body mass index, blood pressure and circulating markers of inflammation and coagulation. Given our approach to control for potential confounding differences between cases and controls in any of these parameters, the present findings support the notion of a relationship between intermittent claudication and cognitive decline which to some extent may be attributed directly to the atherosclerotic process underlying PAD. As pointed out in earlier sections, this would be physiologically plausible since lower-extremity arterial disease is thought to constitute but one marker of chronic, systemic atherosclerosis (Phillips, 2001). In individuals with symptomatic PAD, evidence of atherosclerotic disease in both the coronary and cerebral circulation may be found in as many as 50-90% of cases (Vogt et al., 1992). In addition, the prevalence of carotid atherosclerosis in PAD patients is increased several fold. Even in the absence of overt stroke, atheromatous lesions in either the carotid or intracerebral arteries may be the source of multiple, clinically silent emboli which could induce progressive ischaemic changes in the neural tissue in patients with clinically-manifest atherosclerotic disease. In these individuals, the neurocognitive processes giving rise to general cognitive ability might be particularly sensitive to the influence of such vascular pathological mechanisms. Our finding of a total mediation of the relationship between PAD and decline in domain-specific tests by the general intelligence factor would be supportive of this notion.

In the present study, approximately half of the participants with symptoms indicative of PAD did not have diagnosis of another manifestation of CVD. As a result, our patient group was not mutually exclusive of other vascular conditions although subjects who had suffered a stroke at any point during follow-up were not included. At the baseline and follow-up clinical examinations, the determination of PAD was based on a subject's recall of a doctor's diagnosis of the condition as well as on the administration of the WHO questionnaire. Registration of new vascular events during follow-up was based exclusively on a positive WHO questionnaire response. The WHO questionnaire has been found to lack sensitivity for detecting symptomatic PAD (Fowkes, 1991). Therefore, it is possible that some true cases of PAD went unnoticed in our study. Possibly, this might have occurred under the circumstances where clinical symptoms resolved because of formation of a collateral circulation or any other reason. However, any error whereby diseased subjects would have been misclassified as healthy is likely to have been rare and would have had limited influence on the findings reported here. On the other hand, the associations observed in the present study are likely to reflect the cognitive experience of survivors with mild to moderate vascular morbidity. Indeed, previous studies have reported increased vascular-related mortality in patients with PAD (Dormandy and Murray, 1991), and these may underlie the high attrition rate seen among these patients during cognitive follow-up (Tilvis et al., 2004). The fact that the majority of cases in our study only had probable symptomatic arterial disease might partly reflect the proportionately greater mortality found in patients with more advanced disease. Moreover, only approximately half of those who met the criteria for definite PAD had grade 2 symptoms (onset of leg pain when walking on the level).

6.4. VASCULAR RISK FACTORS AND COGNITIVE DECLINE

6.4.1. Education

The analytical strategy employed in the present study allowed the examination in the total sample of separate relationships of various potentially modifiable CVD predisposing factors with cognitive outcomes, including level of formal education. In several multivariate models, a significant, inverse, linear association emerged between highest completed level of education reported at baseline in 1987/8 and decline in verbal memory performance over the subsequent four-year cognitive follow-up (see tables 21-23) . A further analysis of the data revealed total mediation of the education-verbal memory relationship by general cognitive ability.

Our findings are largely consistent with those already forming a substantial body of literature suggesting early-life educational attainment may be protective against cognitive decline in later-life (Cagney and Lauderdale, 2002; Lee et al., 2003; Seeman et al., 2005). In particular, Cullum et al. (2000) demonstrated that less education was specifically associated with a significantly greater four-year decline in the CAMCOG memory subscale. Other authors have reported significant negative inverse relations of education with decline on multiple domain-specific cognitive measures (Seeman et al., 2005).

Unfortunately, the method of data analysis we used prevented us from examining the relationship between education and performance on the other mental tests that were administered. As a result, we are unable to determine whether the protective effects of education extended to additional cognitive functions in the current sample. On the other hand, we further demonstrated that the association with verbal memory was attenuated so that it no longer remained significant when a general cognitive factor was included in the analysis. It is also possible that the relationship with the cognitive measures could have been attributed to any beneficial effects associated with education on more general or fundamental neurocognitive processes.

Any attempt to account for the observed effects of education on cognitive decline will pose challenges since several possible explanations may exist for such an association. Importantly, our findings existed independently of differences by educational level in demographic structure and baseline cognitive test performance. Also, the multivariate models included terms for clinical CVD, objectively-assessed at any point from baseline to six months prior to follow-up cognitive testing, including PAD and MI as well as a combined category for any non-stroke vascular disease. While an inverse association between education and both CVD mortality (Kilander et al., 2001) and morbidity (Kuper et al., 2006) has been firmly established in the adult general population, in most previous studies examining cognitive function as a primary outcome, CVD status has neither comprehensively nor objectively been determined.

In contrast to these reports, our findings further support an association between education and cognitive decline independently of concomitant CVD, although possible confounding by previous stroke or even asymptomatic vascular pathology cannot be ruled out. However, in this regard, the current results are more in line with a hypothesis suggesting formal education may produce direct effects on brain structure and functioning which, rather than altering the vulnerability to pathological processes leading to cognitive decline, would delay the appearance of clinically-apparent cognitive impairment by furthering the point at which a sufficient amount of pathology had accumulated for symptoms to appear (Albert, 1995).

6.4.2. Body Weight

In the present study, a significant, inverse association between BMI and four-year decline in general cognitive function was found (see table 13). Importantly, the effects of BMI on cognitive decline were independent of differences in age, sex, and prior level of cognitive function. Although significant relationships with body weight have also been reported in a few previous studies, all have been cross-sectional in design. Therefore, a direct comparison with the results reported here is difficult. In particular, despite Kilander et al. (1997) did not find a significant linear association between the BMI and a mean composite score of 13 cognitive function tests, a high BMI was associated with a lower value independently of demographic and socioeconomic factors as well as stroke. Similarly, obesity (BMI $\geq$ 30) in male subjects in the Framingham study was also significantly related to lower global cognitive function (Elias et al., 2005). In addition, several domain-specific subtests of the WAIS scale were also significantly affected. In contrast, any effects of body weight on decline in the individual cognitive measures were not available for study in the current investigation.

The relation between obesity and CVD morbidity is well established (Sacco et al., 1997). However, the association we found with decline in general cognitive ability existed independently of concomitant atherosclerotic vascular disease. Indeed, our multivariate model adjusted for prevalent intermittent claudication which may be a good indicator of the level of systemic atherosclerosis in the body (Vogt et al., 1992). Therefore, although the possibility of confounding by previous stroke cannot be excluded, our findings do not rule out other explanations for our findings. For example, obesity may act as a moderator of the effects of other more proximal vascular risk factors, including high blood pressure (Elias et al., 2001). Indeed, Aleman et al. (2005) failed to find any significant effects of BMI on either mental status or domain-specific tests when a number of well-established CVD risk factors were also included in the multivariate model. Similarly, statistical adjustment for major CVD risk factors attenuated several associations between obesity and cognitive function in the Framingham study so that they no longer remained statistically significant (Elias et al., 2005). However, other relations remained, suggesting different mechanisms could be at work, including inflammatory processes which might be directly related to the endocrine activity of the adipose tissue itself (Jeong et al., 2005).

6.4.3. Smoking

By virtue of the well-established relation of smoking with both cerebrovascular disease (Sacco et al., 1997) and peripheral markers of systemic atherosclerosis (Vogt et al., 1992), the importance of investigations of the potential effects of smoking on cognitive function has been pointed out (Elias et al., 2001). In the current investigation, we found a significant, inverse relationship between pack-years of smoking based on self-report at baseline in 1987/8 and decline in information processing speed estimated from 'best-ever' level of cognitive function to that actually measured in later-life (see tables 29 and 31). Further analyses demonstrated large mediating effects of general cognitive ability on this association.

Although our results seem in conflict with some early cross-sectional reports where cognitive function was examined in relation to smoking status (Elwood et al., 1999), they are also in line with those produced by more recent prospective investigations. For example, Ott et al. (2004) demonstrated that higher baseline pack-year exposure of smoking was correlated with a significantly greater 2.3 year-decline in MMSE-based global cognition among persons aged 65 years and older. Similarly, in a study examining the effects of smoking and midlife cognitive function, associations with a faster decline in verbal memory, slower mental speed and worse concentration were found (Richards et al., 2003). Importantly, these associations proved to be independent of early-life cognitive ability, measured lung-functioning and self-reported CVD. In a similar vein, our findings persisted further to the simultaneous adjustment for demographic factors, estimated prior cognitive ability, mood, blood pressure, and non-stroke CVD. Also, inclusion of inflammatory and haemorheological parameters did not explain away the association.

Although potential confounding by either previous stroke or asymptomatic vascular pathology is hard to rule out, our results raise the possibility of a more direct effect of smoking on the underlying neural substrate. For example, clinical studies have demonstrated smoking can induce a rapid diffuse decrease in cerebral blood flow (Yamamoto et al., 2003). On the other hand, poor nutritional status of smokers has been mentioned as another potential confounder of this association (Richards et al., 2003).

6.4.4. Blood Pressure

It has been suggested that lifetime exposures to elevated blood pressure may be a more important predictor of adverse cognitive outcomes in the elderly than cross-sectionally measured blood pressure levels in old age (Waldstein and Katzel, 2001). Specifically, whereas late-onset high blood pressure may only contribute relatively weakly to cognitive function over and above that of other age-associated morbidity, blood pressure elevation of an earlier onset may result in long-term trajectories contributing to individual differences in adult cognitive decline (Swan et al., 1998; Waldstein and Katzel, 2001). Indeed, associations between blood pressure levels determined in mid-life and poor old-age cognitive outcomes have been reported in several studies (e.g. Kilander et al., 1998; Launer et al., 1995), including the Framingham Study where a dose-response relationship was found between SBP and DBP and performance on tests of both general and domain-specific cognitive functions 12-14 years later when the mean age of the sample was approximately 65 years (Elias et al., 1993).

In a similar regard, the current findings also partly conform to this view given that we found a significant, inverse, dose-response relationship between DBP measured at a single occasion at baseline in 1987/8, when the mean age of the cognitively-tested sample was approximately 62 years, and decline in verbal memory skill over a four-year window of cognitive testing more than a decade later (see table 22). We further showed total mediation of this association by general cognitive ability. Moreover, in another series of analyses, negative yet non-significant associations were found between both DBP and SBP levels and estimated decline in information processing speed from peak, prior cognitive level. Perhaps for the aforementioned reasons, our findings contrast with the null-findings observed by previous studies where both blood pressure and cognitive function in old age have been determined cross-sectionally (Farmer et al., 1987; Scherr et al., 1991).

Whereas the first set of results described above adjusted for age, sex, baseline cognitive scores, education, non-stroke vascular disease and fibrinogen levels, the latter further controlled for several other lifestyle and physiological parameters. In contrast, few studies examining the relation of blood pressure with cognitive outcomes have statistically controlled for concomitant vascular risk factors, CVD, and use of antihypertensives. Although in the present data we cannot exclude the possibility that the presence of either stroke or antihypertensive use might have explained our results (antihypertensive use data were only collected at baseline in 1987-1988 in the EAS), our inability to demonstrate statistically an association with decline in information processing speed in the fully adjusted analysis might in part be attributed to lack of sufficient statistical power.

Additional control for different indices of clinical and asymptomatic vascular disease also led to an attenuation but not disappearance of a significant relationship between mid-life systolic blood pressure and cognitive impairment found in a sample of more than 3000 older men in the Honolulu-Asia Aging Study (Launer et al., 1995). Whereas the above results might suggest a role for blood pressure in cognitive decline independently of atherosclerotic vascular disease, our study was not designed to test different hypotheses underlying such an association. This is likely, however, to be a major challenge for future investigations in this area of epidemiological inquiry.

6.4.5. Blood Viscosity

Our finding of an association between blood viscosity assessed at baseline in 1987/8 and cognitive decline is novel given that few previous population investigations have examined cognitive outcomes in relation to blood rheology. In particular, significant, inverse effects of blood viscosity on the estimated decline in both general cognitive ability (see table 20) and information processing speed (see table 31) from best prior level were found. Further analyses showed that the latter relationship was totally mediated by the effects of blood viscosity on the general cognitive factor. In addition, we observed inverse yet non-significant associations with four-year decline in non-verbal reasoning skill and in decline from peak, prior level in information processing speed when either fibrinogen or haematocrit were also included in the final multivariate model. The statistical adjustment for these factors, both major determinants of blood viscosity, is likely to be the explanation for the absence of significant findings.

Although not directly comparable due to differences in the rheological parameters examined, cognitive measures and study design, our observations are partly in line with those noted in the only previous population-based study to examine this association (Elwood et al., 2001). Although whole blood viscosity was not measured, plasma viscosity, an important contributor to blood viscosity, was significantly and linearly associated with performance on a task of verbal and mathematical reasoning as well as with choice reaction time. On the other hand, a U-shaped association between haematocrit and reaction time was found. Interestingly, fibrinogen did not have significant effects on cognitive performance. Therefore, other determinants of plasma viscosity might possibly play a role in cognitive function, including lipoproteins (Lowe, 2001), although as noted above, our association failed to exist after fibrinogen was statistically controlled for.

Blood viscosity and its determinants have been associated with an elevated risk of both acute coronary events (Yarnell et al., 2004) and stroke (Lowe et al., 1997). The relation with stroke might partly stem from any rheological effects on the pathogenesis of atherosclerotic disease in the carotid circulation (Lee et al., 1998). Importantly, however, in addition to demographic factors and estimated pre-morbid ability level, our associations were also independent of diagnosed stroke. Although silent brain embolism cannot be excluded as a potential link between blood viscosity and cognitive decline, such a relationship might also be mediated through the negative effects of elevated blood viscosity on cerebral blood flow at the microvascular level (Kee and Wood, 1984; Lowe, 2001). Whereas additional research is needed to address the different causal mechanisms likely to underpin the association between blood rheology and cognitive decline, experimental studies are also required where potential modification of rheological parameters in older age groups may result in demonstrable beneficial effects on cognitive outcomes.

6.4.6. Markers of Inflammation and Haemostasis

Relatively few population studies have investigated the association between circulating markers of inflammation and haemostasis and cognitive function. Such a relationship is of interest given the role of inflammation in atherosclerosis and the observed correlations with acute vascular events, including stroke (Chamorro, 2004; Rost et al., 2001). Moreover, a low-grade systemic inflammatory response may contribute to the pathogenesis of degenerative cognitive pathology (Gupta et al., 2005). Despite some contradictory cross-sectional findings, there are observational data showing the risk of cognitive decline may be significantly increased in relation to elevated levels of selected inflammatory markers (Weaver et al., 2002; Yaffe et al., 2003).

Our findings are also largely in line with these results. In particular, in the present study, we demonstrated significant, negative, linear effects of IL-6 determined at baseline in 1987/8 on the estimated decline in information processing speed from peak, prior level after statistical control for demographic factors, vascular disease, mood and a number of physiological parameters (see table 29 and 30). This relationship was further found to be totally mediated by the association of IL-6 with general mental ability.

Furthermore, additional associations were found in a more comprehensive unpublished analysis based on the same sample as examined here (Rafnsson et al., 2007). For example, baseline ICAM-1 was associated with a greater estimated decline from 'best-ever' level in general cognitive function and non-verbal reasoning. Similarly, fibrinogen independently predicted decline in non-verbal intellectual ability. Although not addressed in previous studies, we further showed empirically that the different inflammatory markers were not surrogates but exerted independent influence on the cognitive outcomes. Given the fact that our associations persisted after adjustment for diagnosed stroke, atherosclerosis, and major vascular risk factors, is further suggestive of the possibility that diverse inflammatory pathways may contribute directly to neuropathological changes and cognitive decline.

6.5. POSSIBLE NEUROPATHOLOGICAL SUBSTRATES OF VASCULAR COGNITIVE DECLINE

The identification of likely pathophysiological mechanisms for the association under study constitutes an important aspect of any epidemiological inquiry. The absence of structural neuroimaging in the Edinburgh Artery Study prevented the determination of the potential neuropathological substrates underlying the relationships examined herein. It is likely, however, that vascular risk factors and atherosclerotic pathology may induce diverse changes in the cerebral tissue which, individually or collectively, ultimately may lead to disruption of normal neurocognitive processes. For example, cognitive dysfunction may be the result of ischaemic damage, with or without immediate clinical symptoms, to either the cerebral cortex or grey matter structures located deep within the brain, or both. Also, alterations in the subcortical white-matter, characterised by structural and functional changes in fibres and tracts connecting diverse cortical and subcortical grey matter areas, may induce diffuse changes to higher cortical functioning. Potential neuropathological substrates thought to be associated with vascular cognitive decline are discussed in the following sections.

6.5.1. Cortical Damage

There is published evidence indicating that ischaemic infarcts classified as symptomatic (strokes) tend to comprise relatively large lesions in either the cerebral cortex and/or in deep subcortical grey matter structures (for example the basal ganglia and thalamus). In the general population, approximately one third of clinical strokes occur in the cerebral cortex (Vermeer et al., 2002). While a similar frequency has been described for those affecting subcortical grey matter areas, the same data show that only a very small proportion of cortical infarcts are asymptomatic compared to approximately 80% of subcortical lesions (the neurocognitive consequences of subcortical infarcts are discussed in the next section). These findings suggest that a direct, isolated damage to the cerebral cortex caused by ischaemic infarction is likely to be a major pathological feature underlying neurological and cognitive disturbances in a substantial proportion of stroke patients. On the other hand, in the absence of overt stroke, direct cortical injury may seem a less likely mechanism for impairment of higher cortical functions.

Typically, cortical stroke results in focal or multifocal neurobehavioural deficits, although the range of clinical and neuropsychological findings is likely to reflect, among other things, the vascular territory affected by thrombo-embolic disease, the extent of the ischaemic damage, and its laterality within the brain. Signs of occipital cortical damage, manifest clinically as a spectrum of visual field deficits are, for example, commonly seen in patients with CT/MRI-determined superficial cortical infarction in the posterior cerebral artery (PCA) territory (Cals et al., 2002). In addition, verbal memory deficits may be frequent in these patients, particularly among those with either left hemispheric or bilateral lesions, or large infarcts expanding to other cortical areas. General cognitive function, as determined by the MMSE, may also be impaired in a significant proportion of patients with PCA cortical infarcts, although frequently more so in those with combined cortical and subcortical lesions within this cerebral artery region (Kumral et al., 2004). In patients with stroke in the anterior cerebral artery region, extensive sensorimotor disturbances are common (Kumral et al., 2002). Decreased verbal fluency and executive dysfunction are also frequently observed in such patients, although it is not clear whether such disruptions of higher frontal lobe cortical functioning are the result of ischaemic damage to the cortex per se, subcortical areas, or these combined.

Even in the absence of extensive, multi-lobal, cortical infarcts or ischaemic damage traversing both cortical and subcortical structures, focal cortical lesions may lead to neural dysfunction in both adjacent and distant cortical regions (Brown and Eyler Zorrilla, 2001; Witte et al., 2000). In experimental models, small cortical strokes in the territory of the middle cerebral artery (localised within the parietal lobe) cause an immediate decrease in relative metabolic activity determined with a PET scanner in both the frontal and parietal cortex adjacent to the infarct (Carmichael et al., 2004). Although stroke-induced cortical hypometabolism shows improvement over time, full recovery to pre-stroke levels may not occur, particularly in adjacent cortical areas. The fact that the permanently hypometabolic territory is significantly larger than either the ischaemic lesion or the slightly larger hypoperfused area surrounding the infarct, is strongly indicative of cortical diaschisis. Although this term has been used for any remote effects initiated by a focal cerebral lesion, several different aetiological mechanisms may produce such changes following stroke (Brown and Eyler Zorrilla, 2001). In particular, it is possible that an ischaemic infarction destroys neuronal projections to a remote cortical site, disconnecting it from adequate sources of neuronal innervation. Also, neural functioning distant from the site of infarction may be altered through repetitive neuronal depolarisation that can cross both borders of normal brain tissue and cerebral artery territories to cover an entire cerebral hemisphere (Witte et al., 2000).

In addition to inducing long-lasting cortical hypometabolism, spreading waves of depolarisation may activate multiple molecular cascades in remote areas, characterised by increased microglial activity and upregulation of diverse proinflammatory proteins. Although limited and contradictory evidence exist regarding the independent effects of diaschisis on neurological and neuropsychological outcomes after ischaemic infarction (Bowler et al., 1995; Witte et al., 2000), it is not impossible that such a process, possibly mediated by a neuroinflammatory response, may exist to explain the pattern of generalised deficits in higher mental functions following cortical stroke.

6.5.2. Subcortical Grey Matter Lesions

Further to the above, symptomatic infarcts may involve the subcortex, either in combination with superficial cortical structures or in isolation. With respect to the latter, there is, however, substantial evidence showing that a direct ischaemic injury to subcortical grey matter structures, most commonly the basal ganglia and thalamus, occurs significantly more often without any apparent neurological symptoms (clinically 'silent') (Vermeer et al., 2002; Vermeer et al., 2003). On MRI scanning, subcortical infarcts manifest themselves as areas of focal hyperintensity on T_2-weighted images that are usually less than 15 mm in diameter in the deep territory of small, non-branching end arteries, arising directly from larger cerebral arteries.

It has been suggested that atherosclerosis may contribute directly to subcortical grey matter infarction. For example, microatheromatous vessel pathology may induce lumen stenosis or occlusion of small penetrating arterioles, leading to ischaemia and necrosis. Similarly, an atherothrombotic lesion at the origin of the penetrator, or at the wall of a large, proximal cerebral artery, might lead to an obstruction of its opening. In other circumstances, artery-to-artery embolism or cardioembolism may be suspected as the underlying aetiology in subcortical infarction. In selected samples of stroke patients, between 25 and 40% have had evidence of clinically silent infarcts shown by either CT or MRI scanning (Boon et al., 1994; Corea et al., 2001; Corea et al., 2002; Jorgensen et al., 1994; Mok et al., 2003; Ricci et al., 1993). Even among those with first-ever stroke, between 27 and 38% had evidence of previous asymptomatic brain infarction (Boon et al., 1994; Ricci et al., 1993; Jorgensen et al., 1994). In a sample of 775 consecutive patients with a first-ever cortical stroke, Boon et al. (1994) classified over 80% of all silent lesions as small, subcortical grey matter infarcts.

Asymptomatic infarcts are also common in patients with symptomatic large-vessel disease other than overt stroke. Pardo et al. (1998) described silent brain infarcts in one-third of 100 consecutively admitted stroke-free coronary heart disease patients (mean age 61.3 years), half of which were located in the basal ganglia. Although the number of coronary arteries affected (assessed using coronary angiography) was not related to the presence of silent brain infarcts, the degree of ultrasonographically-determined carotid stenosis was. In another study, the prevalence of MRI-based silent infarcts increased linearly and significantly with the number of major coronary vessels affected by atheromatous lesions (Uekita et al., 2003). Relative to those without significant stenosis of a major coronary artery (the prevalence of silent lesions was 27.3%), the frequency of infarcts in patients with one, two, or three diseased vessels ranged from 55.6 to 81.3%. In addition, both the size and number of silent infarcts was positively and significantly related to the number of affected vessels. In addition, the use of intracranial magnetic resonance angiography (MRA) allowed the determination of both the association of coronary disease severity with intracranial artery atherosclerosis and that of MRA findings with silent infarcts. Significant cerebral artery atherosclerosis was positively related to coronary disease severity and occurred more commonly in patients with infarcts (51.1% in those with brain infarcts versus 6.5% in those without). Furthermore, Hoshide et al. (2001) investigated the occurrence of silent brain infarcts in 208 angiographically-assessed coronary disease patients. In multivariate analyses, the number of diseased coronary arteries independently predicted silent infarcts in the grey matter territories of deep perforating cerebral vessels but not those located in the subcortical white matter. As a result, the authors suggested that, whereas silent brain infarcts in the areas of the deep perforators may partly be caused by subclinical systemic atherosclerosis, those occurring in the white matter might rather be attributed to other aetiological mechanisms, including hypertensive small vessel vasculopathy.

Limited data have been produced on the presence of silent brain infarcts in relation to lower-extremity atherosclerosis, highlighting the need for further research. In a recent small-scale analysis of a relatively young sample (mean age 58.4 years) from the Second Manifestations of Arterial Disease (SMART) Study, Giele et al. (2004) found a non-significant trend toward a greater proportion of subjects with clinically silent brain infarcts also having a low ABPI (ABPI ≤ 0.9). A similar non-significant trend was observed for self-reported history of MI. However, the mean level of intima-media thickness (IMT), possibly acting as a more sensitive marker of atherosclerosis than those above, proved to be significantly higher in those with silent lesions.

In the light of the above, two inter-related questions may be worth asking: although clinically silent, is it possible that deep subcortical infarcts could induce measurable changes in higher cortical functioning as indexed by mental tests? Also, could cognitive deficits in patients with CVD to some extent be attributed to silent brain infarcts? In modestly-sized samples of healthy elderly subjects, the presence of subcortical brain infarctions has been associated (albeit non-significantly) with worse domain-specific cognitive test performance (including perceptual speed, episodic, working, and semantic memory, and visuo-spatial abilities) but not with reduced global cognitive function (based on summarising the scores of all tests) (Schneider et al., 2003). In other cross-sectional-based analyses, silent infarcts determined by MRI and located in the basal ganglia were associated with slower verbal memory retrieval speed and worse executive functioning (O'Brien et al., 2002). Similarly, thalamic lesions were further related to worse focused attention in addition to both slower verbal memory retrieval speed and executive functioning. In the Rotterdam Scan Study, silent thalamic infarcts at baseline predicted a steeper four-year decline in verbal memory performance, whereas non-thalamic infarcts (mostly located in the basal ganglia) were negatively associated with change in psychomotor speed (Vermeer et al., 2003). Also, relative to a single lesion, multiple silent infarcts were more strongly associated with cognitive decline. The effects were restricted to those with incident silent infarcts, irrespective of whether they had silent lesions at baseline, suggesting a stepwise deterioration in higher cortical functioning following silent subcortical infarction.

Although undetermined in non-stroke vascular patients, Sachdev et al. (2004) demonstrated that, in subjects with a history of TIA/stroke, the degree of subcortical grey matter involvement was negatively and significantly associated with a general cognitive factor score, representing the variance shared by the individual mental tests in the study. In contrast, the relation with stroke volume proved not to be significant. This empirical finding prompted the authors to conclude that: "while large cortical strokes do leave a signature on the neuropsychological deficits, they are best regarded as being superimposed on a baseline subcortical pathology." Given the intricate cortico-subcortical circuitry networks connecting the superficial and deep structures, such subcortical infarcts may lead to wide-ranging effects on cortical functioning (Mori, 2002; Tekin and Cummings, 2002). Specifically, up to 20% reduction in metabolism in cortical areas both ipsi and contralateral to unilateral thalamic infarcts has been observed (Baron et al., 1986). Although this pattern is likely to reflect the fact that, in addition to specific systems connecting relay nuclei with specific cortical areas, the thalamocortical connections include non-specific systems that project diffusely into the cerebral cortex, it is unclear how precisely wide-ranging cortical inactivity might come about following a focal thalamic infarction. As a result, Baron et al. (1986) proposed these changes might be due to: a) anterograde degeneration of thalamocortical terminals, b) retrograde degeneration of the corticothalamic neurons, secondary to damage to their thalamic terminals, c) transsynaptic degeneration of the cortical neurons, following damage to the thalamocortical system, or c) reduced activity of cortical neurons without structural damage following the loss of activating afferences from the thalamus.

6.5.3. Subcortical White Matter Changes

Alterations to the subcortical white matter, visualised as bright, hyperintensive periventricular or deep white matter regions on T_2-weighted MRI scans, are frequently observed in neurologically-intact older people. Demonstrated MRI-based hyperintensities have been found in quarter to third of older persons (Breteler et al., 1994; Uehara et al., 1999). Although diverse pathogenic processes may induce changes in the cerebral white matter, most lesions in the elderly are thought to be vascular in origin (Malloy et al., 2005). In clinical samples, more than half of patients with diagnosed stroke have been found to have radiological evidence of white matter hyperintensities (Gerdes et al., 2006). Moreover, an early literature review concluded that white matter lesions were more frequently seen in relation to specific stroke subtypes, such as ischaemic infarction and deep intracerebral haemorrhagic stroke (Leys et al., 1999). Various peripheral markers of atherosclerosis have also been associated with a greater white matter involvement, including both the degree of carotid artery intima-media thickness (Takahashi et al., 2006) and ABPI (Bots et al., 1993). About a fifth of older MI patients had signs of white matter changes, either in periventricular or deep white matter regions (Gerdes et al., 2006). However, in the same study, approximately a third of subjects with intermittent claudication had similar evidence. Furthermore, in the Rotterdam Study, both an ABPI less than 0.9 and possible or definite myocardial infarction were associated with an increased likelihood (OR=2.4 and 3.1, respectively) of cerebral white matter changes (Bots et al., 1993).

Further to vascular disease, potentially modifiable CVD risk factors have been found to be associated with increased white matter hyperintensities, particularly blood pressure level (Waldstein and Katzel, 2001). For example, in population cross-sectional data, clinically-defined hypertension has been related to significantly increased odds of MRI-based white matter lesions (Liao et al., 1996). Moreover, treated uncontrolled hypertensives are found to have greater odds of such lesions than those with treated controlled blood pressure. In a recent prospective study, baseline hypertension was associated with a greater risk of severe white matter hyperintensities at a four-year follow-up (Dufouil et al., 2001). Similarly, de Leeuw et al. (2002) demonstrated greater periventricular and subcortical white matter lesions at follow-up in 60 to 70 year-old subjects diagnosed as hypertensive more than 20 years earlier.

Further evidence of the aetiological role of blood pressure comes from clinical trials showing beneficial effects of active blood pressure lowering on the progression of white matter changes in selected patient samples (Dufouil et al., 2005). Comparatively weaker evidence exists for other risk factors, including smoking, but both smoking status and duration significantly predicted increased periventricular hyperintensities in a selected patient sample of middle aged adults (Fukuda and Kitani, 1996). Similarly, increased BMI was positively related to greater brain atrophy, including of the white matter, in middle aged men and women (Ward et al., 2005). Also, in the Rotterdam Study, both increased coagulation and inflammatory activity were independently and significantly associated with the presence of radiologically-determined white matter abnormalities (Breteler et al., 1994). Whatever the mechanisms, it is thought that the white matter changes seen in relation to vascular risk factors and CVD generally arise from either complete or incomplete ischaemic infarctions and/or hypoperfusion-hypoxic injury due to diverse blood vessel alterations which may include atherosclerosis and thickening (hyalinisation) of deep perforating arterioles (Malloy et al., 2005). These may then induce loss of axons, demyelination, inflammation (gliosis) and necrotic changes which are characteristic neuropathological correlates of vascular-related white matter hyperintensities (Englund, 2002).

The significance of the integrity of the cerebral white matter for higher cortical functioning is well established (Malloy et al., 2005). The burden of white matter hyperintensities was found to be associated with poor performance on cognitive tasks in a recent quantitative review of 23 empirical studies (Gunning-Dixon and Raz, 2000). In particular, greater white matter involvement was related to worse performance in global cognitive function, processing speed, delayed memory and executive functioning. More specifically, hyperintensities in both periventricular and deep regions have been related to a specific decrease in implicit learning of sequences (Aizenstein et al., 2002).

Other studies have associated white matter lesions with a greater decline in aspects of cognitive function, including mental processing speed (van den Heuvel et al., 2006). White matter lesions also contributed significantly and independently of childhood ability level to lifetime decline in general cognitive ability rather than individual mental functions per se (Deary et al., 2003). Moreover, a population study showed that six-year decline in performance on tests of memory, conceptualisation and visuopractical skills was directly related to the progression of white matter lesion burden (Schmidt et al., 2005). Still further evidence comes from studies using diffusion tensor MRI (DT-MRI) where markers sensitive to the ultrastructural integrity of the cerebral white matter have been associated with cognitive outcomes. Thus, Shenkin et al. (2005) showed a strong and consistent, inverse relationship between white matter water diffusion parameters and performance on a non-specific measure of executive functioning. Interestingly, the association was not limited to any of the anatomical regions studied, including the frontal lobe area. Collectively, these reports provide evidence for the influence of white matter hyperintensities on higher cortical functions, particularly those that may be dependent on either speed of processing or the integrity of widely-distributed neural networks (e.g. executive functions) (Gunning-Dixon and Raz, 2000; Malloy et al., 2005).

Importantly, there is currently limited evidence regarding the importance of white matter lesions as a substrate of cognitive deficits in non-demented patients with established atherosclerotic vascular disease. In particular, few studies have examined this association in the context of non-cerebrovascular disease. In contrast, in a small sample (n=96) of older (>75 years) stroke survivors, both the total and frontal volume of white matter hyperintensities correlated significantly and negatively with measures of processing speed and attention (Burton et al., 2004). Moreover, hyperintensities in the region of the temporal lobe were associated with worse memory performance. The strength of the individual associations was modest, however, with the predictor variables explaining between 5 and 10% of the variance in the outcome measures.

Also, in a larger sample (n=323) of consecutively recruited stroke patients, who were administered a comprehensive battery of cognitive tests, total white matter hyperintensities were significantly related to cognitive deficits independently of demographic confounders, infarct volume and cortical atrophy (Jokinen et al., 2005). In particular, performance on tasks assessing processing speed, executive functions, visuospatial ability, visual memory and delayed recall of object learning were affected. In contrast, story-based verbal recall was not related to white matter hyperintensities. An important additional observation was that the association between hyperintensities and memory deficits proved to be either totally or partly mediated by executive function and mental speed, respectively. As a result, these studies also underscore the importance of the integrity of the white matter for both normal processing speed and executive functioning, further to suggesting that impairment in other cortical functions may be secondary to suboptimal functioning of either of these. However, whether such radiological abnormality in the white matter is associated with cognitive decline in these and other vascular patients remains to be explored.

6.6. METHODOLOGICAL ISSUES

Several methodological issues need to be considered in relation to the findings presented above. First, the study sample was recruited from the pool of surviving participants in the EAS who are likely to have differed in several aspects from the representative original baseline cohort. Although a direct comparison with the general population may not be possible, subjects surviving up to follow-up cognitive testing proved to be younger (mean age 63.3 versus 67.6, $P<0.001$), better off socioeconomically (12.8% and 33.8% in social classes I and II compared to 6.6% and 28.4% of non-survivors, P for trend <0.001) and physically healthier (e.g. the stroke prevalence was 1.4% versus 6.2%, $P<0.001$; the prevalence of MI was 2.1% versus 9.1%, $P<0.001$; mean SBP was 141.6 versus 149.7, $P<0.001$; and mean pack-years of smoking were 13.8 versus 23.4, $P<0.001$) at baseline compared to the non-survivors. In addition, only about half of the survivors were eligible for the current study. Of these, approximately two-thirds participated in follow-up cognitive testing. A comparison of tested and non-tested survivors showed those attending cognitive assessment in 2002/3 had lower mean age, less CVD and more favourable vascular risk factor profile at baseline in 1987/8 (see table 1). These participants also had substantially better outcomes on all neuropsychological measures at the baseline cognitive testing in 1998/9 (see table 2).

Second, evaluation of cognitive function was not included in the original EAS protocol and therefore not conducted at the baseline clinical examination in 1987/8. At a later time point during follow-up, a battery of cognitive tests was administered for the first time to surviving participants. Given the already high average age (74.1 years) as well as the size of the sample (n=717) by the time of baseline cognitive assessment, only a modestly-long, subsequent cognitive follow-up was inevitable. Although a longer follow-up would have allowed the examination of a greater magnitude of change in cognitive performance over time, and therefore possibly stronger associations than reported here, there is likely to be an important trade-off between follow-up length and attrition in longitudinal studies of older samples. Partly in order to address this issue, we also estimated cognitive decline over effectively a much longer interval than the actual four-year observational period by including the NART as a covariable in our analyses. In doing so, our data contributed a vastly extended study period, albeit imputed rather than actual, compared to that used in previous investigations for the examination of cognitive decline in relation to CVDs. However, only the difference between NART and scores on the RPM has been validated as a measure of lifetime change in cognitive function (Deary et al., 2004). In contrast, the NART might not have adequately reflected the test elements represented by the other neuropsychological measures we used in the study. Possibly, such a discrepancy between the NART and the other cognitive tests could have contributed to the relatively greater inconsistency in findings in the NART-based models than those where the actual decline from baseline performance was the outcome.

Moreover, the cognitive test battery used in the present study was designed to include widely used, validated measures of major components of human cognition known to be sensitive to the effects of biological ageing and neurological damage. However, only one test was administered for assessing any particular cognitive domain. In this regard, it is likely that only some or limited aspects of what may be considered complex mental functions were actually determined in the present study (Lezak, 1995). For example, only verbal memory but not other memory components, including visual memory and working memory which also may show significant age-associated changes, were assessed. In addition, we measured verbal memory using both immediate and delayed story-based recall but free recall of random words is thought to be cognitively more demanding for older subjects and has solely been used in some previous studies. Similarly, executive functioning was assessed using only a brief, simple measure of word fluency. It is very likely that on its own this test did not adequately reflect the complexity and importance of this particular cognitive domain and that several different executive functioning measures would have been needed. Indeed, the executive functioning domain may be very sensitive to the adverse influence of neurological insults and biological ageing. Possibly as a consequence of the above, few consistent associations with either CVD or vascular risk factors were observed in the present study. In addition, we did not assess other important aspects of human cognitive function, including creativity, which also might be vulnerable to the potentially adverse effects of vascular-induced neuropathological mechanisms. However, in the light of the fact that our outcome data were collected using predominantly brief, easily-administered, simple, single tasks, they are unlikely to fully reflect the magnitude or scope of cognitive deficits experienced by the study sample. Under these circumstances the associations reported herein would underestimate the true level of vascular-induced decelin in general cognitive function in the elderly general population.

Also, our approach to the control for potential confounders of the association between CVDs and cognitive decline was both robust and extensive in comparison to previous studies. However, the information on the majority of covariables we statistically adjusted for was collected at the baseline clinical examination in 1987/8, or more than a decade earlier to the assessment of cognitive functions. Similarly, these acted as predictor variables in our analyses of the relationship between vascular risk factors and cognitive decline. Therefore, two possible consequences of the above need to be considered. Regarding the latter, due to any subsequent random variation or instability in a covariable that was measured at baseline, the associations we report here between vascular risk factors and decline in cognitive function are likely to be conservative estimates. Further to applying to those factors that might have changed over time due to any of a number of reasons (e.g. blood pressure levels, smoking, concentrations of markers of inflammation and coagulation) this could also be of relevance to those covariates for which less accurate methods of measurement existed. On the other hand, regarding our examination of cognitive decline in relation to CVD status where the above covariables were considered as possible confounders, the risk of potential residual confounding by co-existing vascular risk factors might have been increased to an unknown extent.

Other characteristics which also might be thought as potential confounders of the relationships presented here, including cardio -or other vascular surgery and medication history, were not taken into account in our multivariate analyses. With respect to the latter, a detailed structured questionnaire on medication history was administered only at baseline in 1987/8. As a result, up-to-date information on medication use was not available for use in the present analysis. In contrast, at the time of follow-up cognitive testing in 2002/3, subjects were asked open-ended questions about current medication use. When analysed (data not shown) the responses primarily revealed that too few subjects were taking any given type of medication. Therefore, these data were also not used in the current study. As a consequence, however, the possibility of confounding of the associations reported herein by medication use, whereby diseased subjects were more likely to be taking drugs with the capability of interfering with cognitive performance, cannot be ruled out. Similarly, the study findings must be viewed with the possibility in mind that, in some instances, sensorimotor difficulties could have negatively impacted the cognitive test performance of diseased participants (particularly those with a history of stroke when cognitively tested).

Furthermore, as the number of statistical tests conducted was considerable, the probability of a type I error (incorrect rejection of a true null hypothesis) may have been increased (Parker and Rothenberg, 1988). In other words, some of the findings might have occurred from chance alone despite being statistically significant. There is currently no formal consensus on the use of analytical techniques, including the commonly encountered Bonferroni procedures, to control this problem (Nakagawa, 2004; Parker and Rothenberg, 1988). Indeed, it has been pointed out that adjusting statistical significance for the number of tests performed might lead to additional problems, such as an increased likelihood of type II error (incorrect acceptance of a null hypothesis when the alternative is true). Also, the use of such methods may not be appropriate when assessing evidence about specific hypotheses which should better be described and discussed with respect to what tests were conducted, their biological plausibility and in the context of previous research findings (Perneger, 1998; Savitz and Olshan, 1995).

In the current study, the associations examined were specified a priori thus minimising the number of possible comparisons (the possibility of type 1 error was likely to be further reduced by data reduction resulting in the computation of a general cognitive factor). Also, the relationships were generally in the direction expected given the overall similar empirical findings from previous studies and the pathophysiological plausibility of these. Finally, in a majority of multivariate analyses, the associations were reasonably consistent (either statistically significantly or not) across the hierarchical models. Importantly, the significant relationships highlighted and discussed herein were those showing larger effects (and lower significance levels) as these would be more likely to be replicable. In some instances, however, associations either emerged or became stronger when adjusted for further possible confounding factors. While these might have occurred by chance, such an observation could also be an indication of the complexity of the association between vascular pathology and cognitive outcomes.

Finally, to the extent to which vascular-based or other (e.g. AD pathology) neuropathological mechanisms existed to explain our findings, any such processes would in a majority of instances have done so at sub-clinical levels. Specifically, prior to each wave of cognitive testing, GPs would have been expected to exclude any patients with overt dementia although it is possible that some cognitively impaired patients might have been missed despite the screening by GPs. However, it is likely that most patients developing dementia during the four-year cognitive follow-up would have been excluded prior to cognitive assessment in 2002/3. In addition to the above, on both occasions, the MMSE was administered for screening for dementia. In 2002/3, only about five percent of the 452 subjects scored less than 24 on the MMSE, a widely used cut-off point for cognitive impairment. However, preliminary exploration of the data showed that performing poorly on the MMSE was not related to CVD status.

6.7. CHAPTER SUMMARY

The major findings of the current study are that both atherosclerotic vascular diseases and risk factors are associated with a modest yet progressive decline across diverse cognitive functions in older survivors from the general population. In particular, stroke was related to an accelerated decline in both general ability (0.32 to 1.25% of the total variance was explained by stroke) and verbal memory skill (stroke accounted for 1.21% of the total variance). In the absence of overt stroke, MI was associated with a steeper decline in non-verbal reasoning (and accounting for about 0.90% of the total variance) but angina did not predict cognitive decline in the present sample. Peripheral arterial disease was also associated with an increased decline in both general cognition and verbal memory (accounting for about 0.29 and 0.88% of the total variance, respectively). Several established as well as novel vascular risk factors were also associated with a greater decline in neuropsychological test performance.

The present findings further add to those previously demonstrating an association between vascular diseases and cognitive impairment and decline in global cognitive function and across restricted sets of mental abilities (Elwood et al., 2002; Haan et al., 1999; Singh-Manoux et al., 2003; Zhu et al., 1998). The results also contribute to the still limited literature available on the relation of novel CVD risk factors with cognitive function of older people. Specifically, the inverse associations of both markers of inflammation and coagulation, and blood viscosity with decline in domain-specific cognitive tests are new. The robust control for a large number of potentially confounding factors of the associations between atherosclerotic CVDs and cognitive decline suggest these relationships may in fact depend on the underlying pathological process. Similarly, the observed independent effects of vascular risk factors also favour distinct negative influences on neurocognitive processes. The unavailability of structural neuroimaging in the present study prevented the determination of the neuropathological changes likely to underlie these relationships although both the effects of CVD and risk factors with decline in individual mental tests were either totally or largely mediated through the relationship of these with general cognitive function. To the extent to which general intelligence is thought to reflect neurocognitive processes that depend on intact deep white and grey matter integrity, the findings point in the direction of subcortical pathology as a major neuropathological substrate associated with cognitive decline in the current sample.

In the final chapter of this thesis, the major implications of the current findings are discussed. Moreover, recommendations for future research are presented which are based on the current results as well as the review of past investigations examining the associations between vascular diseases, risk factors and cognitive function of older people.

CHAPTER SEVEN

Implications, Recommendations and Conclusions

7.1. IMPLICATIONS

The main implications of the present study and of previous research of the association between CVDs, vascular risk factors and cognitive function in the elderly, relate to the potential value of controlling or preventing vascular risk factors and diseases in order to preserve the cognitive health of older age groups. Regarding the associations with individual CVD risk factors, the results might also inform strategies aimed at reducing or preventing cognitive decline through blood viscosity reduction, neuroprotection and the facilitation of cognitive reserve in older people. However, it must be borne in mind that any cognitive effects of individual CVDs and vascular risk factors are generally very modest and the need for identifying yet other potentially modifiable risk factors for cognitive decline (which may contribute to individual differences in cognitive decline to a greater extent) is still unmet. On the other hand, from a public health point of view, it is importance to acknowledge the fact that several risk factors may be present in old people and their effects on cognitive function may be cumulative (see point 1 in section 7.2 below).

In particular, the present findings would support strategies aimed at the primary prevention of cardiovascular morbidity through the reduction of levels of major CVD risk factors. At the general population level, the use of full range of primary preventive measures to reduce smoking and to lower population blood pressure and serum cholesterol levels might not only decrease the total burden of CVD in society but possibly also lead to the control of other chronic conditions which share the same risk factors (Beaglehole and Dobson, 2005; Purandare et al., 2005). Specifically, the magnitude of benefit against CVDs achievable through diet and lifestyle modification may be large and may outweigh that resulting from the medical treatment of either elevated blood pressure or cholesterol levels (Hu and Willett, 2005). With respect to cognitive impairment and decline, reducing the cardiovascular morbidity (particularly if the cumulative effects of several risk factors are addressed) in older people might slow down the deterioration in mental function and/or delay or prevent the onset of cognitive impairment (Gow and Gilhooly, 2003; Purandare et al., 2005). Moreover, based on the current results, it is possible that further to reducing the progression of atherosclerosis and its potential effects on the neural substrate, CVD risk factor lowering per se might prove beneficial for the neuropsychological functioning of older persons. Any positive effects of such efforts might be realised most clearly in relation to efforts to deliberately lower elevated risk factor levels in older people at high absolute risk of a cardiovascular event.

In persons with established atherosclerotic CVDs, the risk of recurrent vascular events in the same or different arterial beds is significantly increased. The secondary prevention of further vascular episodes in these patients is of major importance and aggressive treatment of potentially modifiable CVD risk factors, irrespective of their level, has been advocated for this purpose (Anand et al., 2005). In people with stroke, for example, treatments for the prevention of repeated events are well established and, in addition to antihypertensive medication, include the use of antiplatelet agents, carotid endarterectomy and warfarin for atrial fibrillation (O'Brien et al., 2003). In the present study, older non-demented subjects with symptomatic CVDs were further found to be more vulnerable to cognitive decline relative to those without major vascular morbidity. Importantly, both the presence of stroke as well as clinically-manifest coronary and peripheral atherosclerosis was associated with an increased decline in cognitive function. Despite being strong predictors of subsequent vascular events in CVD patients, high blood pressure, smoking, atrial fibrillation, elevated blood glucose and cholesterol levels may not be significant predictors of the level of cognitive function in people with stroke (Sachdev et al., 2006). Similarly, in selected samples of stroke-free patients with advanced lower-extremity arterial disease, the extent or severity of disease may be a more important predictor of cognitive function than conventional CVD risk factors (Phillips, 2001). These findings could imply that the part played by known CVD risk factors in cognitive decline is predominantly that related to the promotion of atherosclerotic disease which, once manifested clinically, assumes the role of the major vascular mechanism underlying cognitive decline in CVD patients. In turn, these results further highlight the importance of both the primary prevention of

CVDs in healthy adults as well as of those approaches needed to reduce or reverse the progression of atherosclerosis in older vascular patients in order to preserve cognitive health.

A novel finding in the current study was the inverse relationship observed between blood viscosity and decline in cognitive function. Possibly, age-related increases in blood viscosity disrupt cognitive processes by inducing chronic reductions in the cerebral blood flow of older people. These findings highlight the importance of strategies aimed at identifying and treating older persons for increased viscosity with the aim of improving levels of cognitive function (Lowe, 2001).

Further to the above, additional ways to either enhance neuroprotection or build up cognitive reserves may be the focus of other strategies aimed at maintaining cognitive health in later-life (Purandare et al., 2005). For example, reducing stress levels, engaging mentally, exercising regularly and adopting a healthy diet have been advocated as important low-risk strategies for the maintenance of brain health of older people (Small, 2002). Also, evidence from observational epidemiological studies suggests that use of antioxidant vitamins and non-steroidal anti-inflammatory agents (NSAIDs) may be associated with a lower risk of cognitive impairment (Purandare et al., 2005). Ageing is accompanied by increased immune dysregulation and circulating proinflammatory molecules may play a key role in chronic brain inflammation and neurodegeneration (Solfrizzi et al., 2006). In the current study sample, circulating markers of inflammation were associated with decline in cognitive function. Possibly, inhibition of key components of the inflammatory response with the aid of NSAIDs may offer neuroprotective effects resulting in reduced cognitive decline in non-demented individuals found at an elevated risk. Furthermore, we demonstrated that more formal education was associated with less cognitive decline in adult life. Despite the exact mechanisms of this relationship remain unknown such an observation may still have practical implications. In particular, it has been suggested that increased levels of education in the general population at large might lead to lessening of the burden of cognitive impairment and decline (Albert, 1995).

7.2. RECOMMENDATIONS FOR FURTHER RESEARCH

The current study raises a number of questions that need to be addressed in future research of vascular-related cognitive decline in older people. These are presented and discussed each at a time below.

1) More observational research is required to examine the potential impact of modifiable atherosclerotic risk factors on change in different cognitive functions in representative samples of patients with established vascular diseases. Previous studies have been few and mainly focused on post-stroke cognitive impairment (Sachdev et al., 2006). On an individual basis, vascular risk factors may not contribute independently, or only weakly, to cognitive function in the presence of clinically-manifest atherosclerotic disease (Phillips, 2001). However, there is limited evidence suggesting that the overall CVD risk factor exposure in vascular patients may be associated with impaired cognitive function (Sachdev et al., 2006). Therefore, in future studies, the possible cumulative impact of multiple risk factors on diverse aspects of neuropsychological functioning needs to be evaluated in relation to different cardiovascular morbidity types. The importance of such research is further emphasised in the light of empirical data showing CVD risk factors tend to be largely undertreated and undercontrolled in CVD patients (Bhatt et al., 2006) and relatively more so in relation to PAD than CHD (McDermott et al., 1997).

2) Further studies are needed in order to better understand how different pathological indices of cardiovascular morbidity may be associated with neuropsychological functioning and decline in CVD patients. For example, in selected samples of patients with symptomatic lower-extremity arterial disease, disease severity has emerged as a relatively important predictor of cognitive function (Phillips, 2001). Similarly, haemodynamic pressure variables (i.e. pulmonary artery pressure) and cardiac output have been associated with worse pre-operational cognitive test performance among cardiac transplant patients (Putzke et al., 1998). It is of importance that similar work is replicated in large, representative population samples

involving older survivors with clinical CVD in different arterial territories in the body.

3) Now that evidence showing greater cognitive impairment and accelerated mental decline in older survivors with vascular diseases is accumulating, it is imperative that further studies characterising the substrate possibly underlying such findings are conducted. Although still limited, previous studies have highlighted the importance of MRI-detected sub-cortical white matter changes for post-stroke neuropsychological function (Burton et al., 2004; Jokinen et al., 2005; Sachdev et al., 2004). Identical work needs to be carried out on larger samples of community-based stroke survivors recruited from different populations. Also, an important gap exists with respect to the relation between structural imaging and outcomes on neuropsychological tests in patients with non-stroke vascular diseases that needs to be filled. The careful assessment of both the location and severity of brain lesions as well as the detailed examination of cognitive functions must be the minimum. Furthermore, where possible, future studies should also consider the use of more sensitive techniques (i.e. diffusion tensor MRI) for the measurement of cerebral white matter integrity in order to determine the potential cognitive impact of early or very small changes in the white matter structure.

4) Intact cognition remains a critical dimension of the health of older people yet few studies have examined real-life functioning in relation to subtle neuropsychological deficits. In particular, there is currently a great need for additional research regarding how change in neuropsychological test performance might influence everyday functioning of high-risk populations, including CVD survivors. Based on data from small clinical samples, performance on tests of visuospatial ability, memory and attention may be predictive of informant-reported, everyday adaptive functioning in patients with advanced-level peripheral arterial atherosclerosis (Phillips, 1996). The potential effects of subtle decrements in different cognitive functions on everyday activities such as driving, reading and adherence to medical regimens would need particular attention in future studies.

5) Further prospective data are required in order to determine the predictive value of subtle changes in neuropsychological performance for further ongoing cognitive deterioration and dementia onset in older vascular patients. In particular, information is needed regarding the value of changes in specific neuropsychological domains in predicting future cognitive impairment. In samples of community-resident elderly, poor performance on aspects of memory may be predictive of future dementia (Grober et al., 2000) but similar data are lacking from survivors with CVD. In addition, the clinical significance of cognitive function decline for other adverse events, including mortality and institutionalisation, needs to be investigated in older people with vascular diseases.

6) The greatest potential for halting or delaying cognitive decline in older adults may be tied to the adequate prevention and control of cardiovascular risk factors (Román, 2003). The major emphasis placed on the cognitive effects of elevated blood pressure levels and diabetes in neuroepidemiological investigations needs to continue (Elias et al., 2001). Future studies need to resolve the current controversy regarding the association between hypertension and cognitive function by focusing on methodological issues such as the definition and measurement of hypertension and cognitive decline and the choice of study population. In addition, potential confounding by comorbidity and medical treatment needs to be adequately addressed in older samples (Birns and Kalra, 2006). With respect to research of cognitive function in adult diabetics, the need for agreed standards of study design and a consensus on a core battery of neuropsychological tests has been highlighted (Strachan et al., 1997). The possible role of other modifiable risk factors, including smoking, obesity and cholesterol, needs much further attention in large-scale prospective studies. In particular, the combined impact of several vascular risk factors should be investigated.

There is also much needed research on neuropsychological functioning in relation to other less established vascular factors, including markers of inflammation and coagulation, blood rheology, plasma homocysteine, and low B-vitamin levels (Elias et al., 2001). The detailed quantification of the potential impact of these factors on cognitive functions would ideally need to be performed in well-powered, prospective, population studies where data on different aspects of cognitive function were also gathered. Moreover, the collection of structural imaging data would also provide valuable information on the nature of the cerebral changes underlying cognitive decline associated with unfavourable risk factor levels. A further strand of research would be based on examining the possible interaction or synergism between these exposures and common polymorphisms (e.g. apolipoprotein E ε4, APOE ε4) on the rate of mental decline in the elderly. Such study might further facilitate the stratification of older people who may be at an increased risk of cognitive decline (Haan et al., 1999).

7.3. CONCLUSIONS

Cognitive function represents a vital component of the health status of older people. Observed age-related decrements across various cognitive abilities may in part be attributed to influence of cardiovascular risk factors and systemic atherosclerotic diseases which increase in frequency with age. Despite this, cognitive impairment and decline has been an understudied outcome in cardiovascular epidemiological research. In particular, few population studies have prospectively examined change in neuropsychological function in older people with clinically-manifest vascular diseases, taking into account potential confounding effects of multiple co-existing sociodemographic and atherosclerotic risk factors. Also, vascular risk factor research has hitherto focused on cognitive function in relation to a few established exposure variables while largely ignoring the potential impact of several other conventional and novel vascular risk factors.

The present thesis described findings based on an investigation of the associations between vascular diseases, risk factors and longitudinal change in cognitive test performance in a population-based sample of older survivors with vascular diseases.

The results showed that stroke was associated with a significantly steeper decline in both general cognitive function, as indexed by a general cognitive factor representing the variance common to all the cognitive tests used, and verbal memory over a four-year follow-up. When decline was estimated from peak, prior cognitive level, stroke was related to a greater decline in both general cognition and verbal fluency. Similarly, general cognition and most individual mental tests were negatively affected in subjects with CVD other than stroke. With respect to the specific non-stroke vascular morbidity groups, accelerated four-year decline in non-verbal reasoning ability was noted in relation to MI but angina was not associated with cognitive decline in this study. Subjects with PAD also experienced a faster decline in both general cognition and verbal memory over the four-year follow-up.

Several potentially modifiable vascular risk factors were also related to a greater cognitive decline. In particular, significant associations were observed with body mass index, smoking, diastolic blood pressure, inflammatory markers and blood viscosity. In contrast, more formal education in early life was related to less cognitive decline.

The associations with CVDs were found to be independent of major potential confounding factors. The findings therefore suggest that the progressive cognitive decline in both stroke and non-stroke survivors might in part be attributed to the underlying atherosclerotic process. Similarly, CVD risk factors were associated with cognitive decline independently of clinical markers of atherosclerosis. In this context, both atherosclerosis and risk factors may induce neuropathological changes in sub-cortical structures which lead to progressive deficits in higher cortical functioning. Possibly, alterations to complex neural networks and/or interneuronal connectivity following damage to deep sub-cortical grey and white matter structures may mediate the association between vascular pathology and neuropsychological function. The finding that decline in performance on specific mental tests was principally accounted for by the impact of CVD and risk factors on general cognitive ability, rather than on the individual functions per se, might lend further support to such a notion.

The results also bring up several questions that need to be addressed through further research. Specifically, future studies need to examine the potential impact of multiple vascular risk factors on cognitive decline in CVD patients. Further understanding of predictors of cognitive function in such patients must come from studies collecting data on various aspects of the underlying vascular pathology. The use of neuroimaging is imperative if understanding of the neuropathology underlying vascular cognitive decline is to be gained. In addition, it is important to determine through further study the clinical relevance subtle cognitive decrements may have for older vascular patients. Exposures to atherosclerotic risk factors need to be quantified in relation to neuropsychological functioning of older people. There is much scope for further research involving novel risk factors and of the potential synergism genetic-environmental interactions may show in increasing risk for cognitive decline. Despite the challenges posed by the above with respect to time and funding, the true test of aetiological research is likely to be the extent to which the knowledge generated can be utilised to halt or delay cognitive decline in both at-risk individuals and the elderly general population at large.

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APPENDIX A: Characteristics of studies investigating cognitive performance in relation to cardiovascular disease

A-1: Stroke and cognitive performance

Author and publication date	Sample	n	Age	Design	Case/Morbidity Type	Cognitive Measure	Outcome
Tatemichi et al. (1994)	Clinic	227/240	70.6/70.8‡	Cross-sectional	Ischaemic stroke	SRemT, BVRT, MMSE, BNT, BDAE, WAIS-R, Rose Drawing Test, MDRS	Verbal/visual memory, orientation, language, attention
Desmond et al. (1996)	Clinic	151	70.4†	Longitudinal	Ischaemic stroke	SRT, BVRT, MMSE, BNT, BDAE, WAIS-R, Rose Drawing Test, MDRS	*No comparison with non-stroke controls*
Kalmijn et al. (1996)	Community	353	69-89	Longitudinal	Stroke/TIA	MMSE	Global functioning
Zhu et al. (1998)	Community	1810	≥75	Cross-sectional	Stroke	MMSE	Global functioning
Kase et al. (1998)	Community	74/74	78.6/78.7‡	Longitudinal	Stroke/TIA	MMSE	Global functioning
Hochstenbach et al. (1998)	Clinic	229/33	55.9/52.4‡	Cross-sectional	Stroke	AVLT, WAIS, RBMT, Trail Making Test A/B, BIT, Money's Road Map Test, Bobertag, DAS, VFT	Processing speed, long-term memory, visuospatial- constructive ability, language, arithmetic, attention

Haan et al. (1999)	Community	5888	≥65	Longitudinal	Stroke/TIA	MMSE, DST	Global functioning, psychomotor speed
Dik et al. (2000)	Community	1224	62-85	Longitudinal	Stroke	MMSE, AVLT, Coding Task	Global functioning
Madureira et al. (2001)	Clinic	237	59†	Cross-sectional	Stroke	MMSE, Five words recall, letter cancellation, VFT, Motor altering sequences, WMS, Object nomination, words and sentences, Token test, Orientation test, WAIS, Buccofacial and limb verbal commands, Clock drawing, Draw by copy, Arithmetic operations, RPM, Proverb interpretation	*No comparison with non-stroke controls*
Tham et al. (2002)	Clinic	252	60.3†	Longitudinal	Ischaemic stroke/TIA	Digit Span, Visual Memory Span, ADT, BNT, VFT, Verbal and Visual Memory Tests, WMS-R, Clock Drawing Test, WAIS-R, Maze Task	*No comparison with non-stroke controls*
Ballard et al. (2002)	Clinic	150	≥75	Cross-sectional	Stroke	CAMCOG, CDR	Global functioning, processing speed, working memory, executive functions
Rasquin et al. (2002)	Clinic	139	69.3†	Longitudinal	Stroke	AVLT, Concept shifting task, SCWT, CAMCOG	*No comparison with non-stroke controls*

Patel et al. (2002)	Community	645	All ages	Cross-sectional	Stroke	MMSE	*No comparison with non-stroke controls*
Patel et al. (2003)	Community	163	All ages	Longitudinal	Stroke	MMSE	*No comparison with non-stroke controls*
Srikanth et al. (2003)	Community	99/99	70.5/69.9‡	Cross-sectional	Stroke	WAIS-R, K-SNAP, MMSE, RAVLT, RBMT, RCFT, Clock Drawing test, COWAT, IQCODE	Attention, spatial ability, language, executive ability
Ballard et al. (2003)	Clinic	115	≥75	Longitudinal	Stroke	CAMCOG, CDR, BNT, VFT, MMSE	*No comparison with non-stroke controls*
Ballard et al. (2003)	Clinic	150/30	79.2/77/6‡	Cross-sectional	Stroke	CAMCOG, CDR, SRT, CRT, VIG	Information processing speed, attention, executive functions, working memory
Rasquin et al. (2004)	Clinic	196	68.4†	Longitudinal	Stroke	CAMCOG, AVLT, CST, SCWT, GIT, Mental Rotation	Information processing speed, calculation
Riepe et al. (2004)	Clinic	209	69.8†	Longitudinal	Ischaemic stoke	ADAScog, MIS, Letter Sorting Test	*No comparison with non-stroke controls*
Sachdev et al. (2004)	Clinic	128/78	72.0/70.6‡	Longitudinal	Ischaemic stroke/TIA	WMS-R, WAIS-R, BNT, Trail Making Test A/B, WAB, Lexical/Semantic VFT	Verbal memory, visuo-constructive ability
Lindén et al. (2004)	Clinic	149/745	81.0/81.3‡	Cross-sectional	Stroke	ADAScog	Abstract reasoning, memory

Sachdev et al. (2004)	Clinic	170/96	72.1/71.3‡	Cross-sectional	Ischaemic stroke/TIA	WMS-R, WAIS-R, SDMT, WAB, Trail Making Test A/B, Color Form Sorting Test, Lexical/Semantic VFT, Annett's Test, NART	Visual memory, executive functions, abstract reasoning, visuo-constructive ability, information processing speed
Zhou et al. (2005)	Clinic	434	67.6†	Cross-sectional	Ischaemic stroke	MMSE, IQCODE	*No comparison with non-stroke controls*
Elkins et al. (2005)	Community	9704	≥ 60	Longitudinal	Stroke	MMSE, DST, Trail Making Test B	Global functioning, executive functions, attention

*ADAScog=Alzheimer's Disease Assessment Scale; ADT=Auditory Detection Test; BIT=Behavioural Inattention Task; BVRT=Benton visual retention test; BDAE=Boston Diagnostic Aphasia Examination; BNT=Boston Naming Test; CAMCOG=Cambridge Examination for Mental Disorders of the Elderly; CDR=Cognitive Drug Research computerised system; CRT=Choice reaction time; CST=Concept-Shifting Task; COWAT=Controlled Oral Word Association Test; DST=Digit Symbol Test; VIG=Digit vigilance; DAS=Dutch Aphasia Society; GIT=Groninger Intelligence Test; IQCODE=Informant Questionnaire for Cognitive Decline in Elderly; K-SNAP=Kaufman Short Neuropsychological Assessment; MDRS=Mattis Dementia Rating Scale; MIS=Memory Impairment Screen; MMSE=Mini-Mental State Examination; NART=National Adult Reading Test; RPM=Raven's Progressive Matrices; AVLT=Rey's Auditory-Verbal Learning Test; RCFT=Rey's Complex Figure Test; RBMT=Rivermead Behavioural Memory Test; SRemT=Selective Reminding Test; SRT=Simple reaction time; SCWT=Stroop Colour Word Test; VFT=Verbal Fluency Test; WAIS-R=Wechsler Adult Intelligence Scale; WAB=Western Aphasia Battery; WMS-R=Wechsler Memory Scale-Revised.

†Mean age of the total number of study subjects/cases. ‡Mean age of cases and controls, respectively. †Results are based on comparing patients with stroke to non-stroke controls.

A-2: Coronary heart disease and cognitive performance

Author and publication date	Sample	n	Age	Design	Case/Morbidity Type§	Cognitive Measure*	Outcome
Barclay et al. (1988)	Clinic	20	72.5†	Cross-sectional	Rehabilitation patients	MMSE, MSQ, WAIS-R, Mattis Dementia Rating Scale, Purdue, PEG, Naming Test	*No comparison with non-CVD controls*
Hale et al. (1992)	Community	1217	78.0/77.8[ª]	Cross-sectional	ECG codes	MMSE	*No comparison with non-CVD controls*
Breteler et al. (1994)	Community	4971	55-94	Cross-sectional	Presence of MI	MMSE	ND*
Petrovich et al. (1998)	Community	3734	71-93	Cross-sectional	History of MI	CASI	NS
Zhu et al. (1998)	Community	924	≥75	Longitudinal	CHD/Heart Failure	MMSE	NS
Ahto et al. (1999)	Community	486	≥64	Cross-sectional	CHD	MMSE	NS

Haan et al. (1999)	Community	5888	≥65	Longitudinal	ECG/Heart Failure	MMSE, DST	NS
Moser et al. (1999)	Clinic	129	60.9/67.6‡	Cross-sectional	Rehabilitation patients	MMSE, RMT-W, Similarities, DST, BNT, Animal Fluency	NS
Putzke et al. (2000)	Clinic	88	48.5/44.8‡	Cross-sectional	Transplant candidates	SILS-AB, SILS-VOC, PEG, Trail Making Test A/B, LMT, CATS, WRA	Psychomotor speed, mental flexibility, abstract reasoning, problem solving, fine motor speed and dexterity
Elwood et al. (2002)	Community	1700	55-69	Cross-sectional	Angina/ECG/MI	MMSE, CAMCOG, AH4	Global functioning, verbal and mathematical reasoning, reaction time
Eslinger et al. (2003)	Community	287	75.7†	Longitudinal	CHD	MMSE	NS
Piguet et al. (2003)	Community	377	80.4†	Longitudinal	CHD	MMSE	NS
Selnes et al. (2003)	Clinic	232	63.4/65.8‡	Cross-sectional	CABG candidates	MMSE, BNT, AVLT, Trail Making Test A/B, PEG	NS
Singh-Manoux et al. (2003)	Community	5822	46-68	Cross-sectional	Angina/MI/CHD	Short-term memory test, AH4, Mill Hill Test, VFT	Verbal memory, verbal and mathematical reasoning, knowledge, recognition and comprehension

Verhaeghen et al. (2003)	Community	516	70-103	Longitudinal	MI/CHD/Heart Failure	Digit Letter and Identical Pictures, Paired Associates and Memory for Text, VFT, Vocabulary and Spot-a- Word	Composite intelligence, perceptual speed, executive functioning, semantic memory
Tilvis et al. (2004)	Community	650	75,80,85¶	Longitudinal	History of MI/Heart Failure	MMSE	Global functioning

§ECG=Electrocardiograph; MI=Myocardial Infarction; CHD=Coronary Heart Disease; HF=Heart Failure; AF=Atrial Fibrillation; CABG=Coronary Artery Bypass Graft. *BNT=Boston Naming Test; CAMCOG=Cambridge Examination for Mental Disorders of the Elderly; CASI=Cognitive Abilities Screening Instrument; DST=Digit Symbol Test; LMT=Logical Memory Test; MSQ=Mental Status Questionnaire; MMSE=Mini-Mental State Examination; PEG=Pegboard Test; RMT-W=Recognition Memory Test-Words; SILS=Shipley Institute of Living Scale; CATS=Short Category Test; VFT=Verbal Fluency Test; WAIS-R=Wechsler Adult Intelligence Scale-Revised; WRA Test=Wide Range Achievement Test.†Mean age for total number of study subjects/cases. ‡Mean age for cases and controls, respectively. ⁿMean age for male and female subjects, respectively. ¶Birth cohort age.†Results are based on the difference between cases and controls, or in the case of multiple markers of CHD, any that is statistically associated with at least one cognitive measure at the 5% significance level. ‡All results statistically non-significant. *No data on statistical significance testing.

A-3: Peripheral atherosclerosis and cognitive performance

Author and publication date	Sample	n	Age	Design	Case/Morbidity Type	Cognitive Measure*	Outcome
Hertzog et al. (1978)	Community	156	73-80	Longitudinal	Atherosclerosis	PMA (verbal meaning, space, reasoning, number, word fluency), TBR (motor-cognitive rigidity and psychomotor speed)	Spatial and numerical ability, IQ, psychomotor speed
Pinzur et al. (1986)	Clinic	60	60.3†	Cross-sectional	Leg amputees	TMFE, AVLT, RCF	*No comparison with non-vascular controls*
Shaw et al. (1987)	Clinic	50	57.4†	Cross-sectional	PAD surgery candidates	Trail Making Test B, WMS, WAIS	*No comparison with non-vascular controls*
Phillips et al. (1993)	Clinic	14	67.4†	Cross-sectional	PAD amputees	WMS-R, WAIS-R, RCF, RMTFW, GNT, COWAT, MCST	Psychomotor speed, problem solving, abstract reasoning
Breteler et al. (1994)	Community	4791	55-94	Cross-sectional	APBI<0.9/ Carotid stenosis	MMSE	General cognitive function
Auperin et al. (1996)	Community	1279	59-71	Cross-sectional	Carotid stenosis/IMT	MMSE, Trail Making Test B, WAIS-R, PASAT, BVRT, WFT, RPM	*No comparison with non-vascular controls*

Phillips and Mate-Kole (1997)	Clinic	29	64.8†	Cross-sectional	ABPI<0.8/PAD amputees	WCST, COWAT, WFT, WAIS-R, CVLT, Digit Span, RCF, Trail Making Test A/B, GNT, PEG, TPD	Attention, psychomotor speed, executive functioning, visuospatial ability, visual memory
Iddon et al. (1997)	Clinic	30/30	64.0/64.3‡	Cross-sectional	Carotid stenosis (≥70%)	MMSE, VFT, CANTAB, Pattern and Spatial recognition, Spatial Span, Spatial Working Memory Task, Attentional Set Shifting Paradigm, PALT, Simultaneous and Delayed Matching to Sample	NS
Haan et al. (1999)	Community	~5000	≥65	Longitudinal	ABPI<0.9/Carotid stenosis	MMSE, Digit Symbol Test	Psychomotor speed
Rao et al. (1999)	Community	25	≥65	Cross-sectional	Intermittent claudication/ Carotid stenosis	CAMCOG, Trail Making Test A/B, BDCS, COWAT	NS (IC) *No comparison of carotid disease with non-vascular controls*
van Exel et al. (2002)	Community	596	85†	Cross-sectional	Atherosclerosis	MMSE, Digit-Coding Test, Stroop Test, WLT	*No comparison with non-vascular controls*

Elwood et al. (2002)	Community	1700	55-69	Cross-sectional	Intermittent claudication	MMSE, CAMCOG, AH4, CRT	NS
Waldstein et al. (2003)	Community	38	69.8†	Cross-sectional	Clinical PAD	WAIS-R, WMS-R, Trail Making Test A/B, Stroop, PEG, JOLT	Non-verbal memory, concentration, perceptual-motor speed, manual dexterity and executive functioning
Piguet et al. (2003)	Community	377	80.4†	Longitudinal	Intermittent claudication	MMSE	NS
Fearn et al. (2003)	Clinic	159/20	68.0/N/A‡	Cross-sectional	Carotid stenosis (≥70%)	CDRCAS	*No comparison with non-vascular controls*
Aharon-Peretz et al. (2003)	Clinic	22/14/24	68.6/63.2/65/8‡	Cross-sectional	Carotid endarter-ectomy candidates	MMSE, TOL, Trails Making Test, WCST, PEG, RAVLT, Digit Span, RAVLT, CBTT, RCF	Attention, Visual searching, Processing speed, Verbal learning

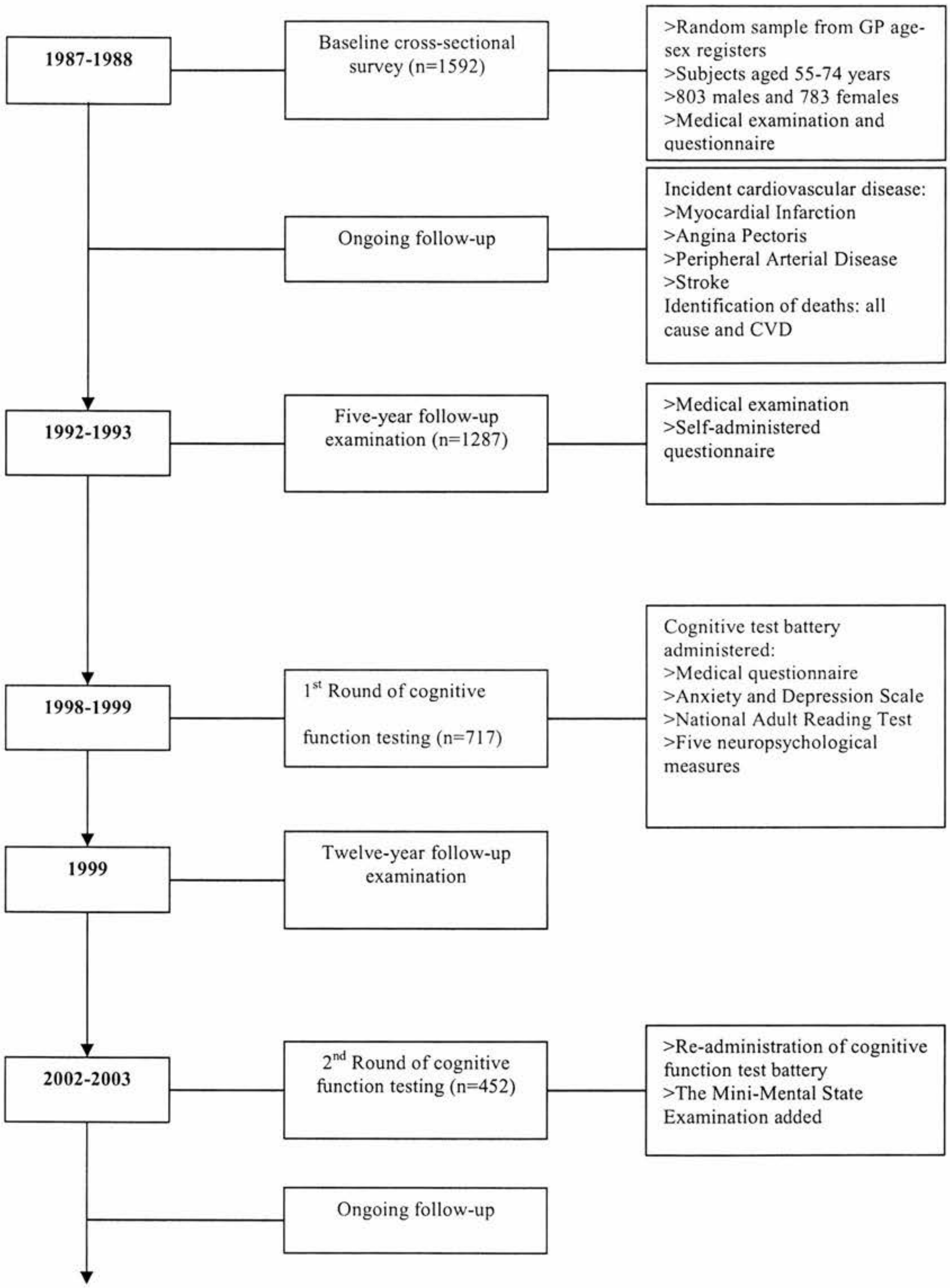
Singh-Manoux et al. (2003)	Community	5822	46-68	Cross-sectional	Intermittent claudication	Short-term memory test, AH4, Mill Hill Test, VFT	Verbal memory, verbal and non-verbal reasoning, knowledge, comprehension, lexical and semantic verbal fluency
Kishikawa et al. (2003)	Clinic	23/17	68.0/66.6‡	Cross-sectional	Carotid endarter-ectomy candidates	MMSE, HDSR, Kohs block-design test, BVRT, word recall	*No comparison with non-CVD controls*
Brand et al. (2004)	Clinic	36	63.3†	Cross-sectional	Carotid endarter-ectomy candidates	Dichotic listening, Finger tapping test, Motor planning test, VFT, Complex figure test copy	Auditory processing, psychomotor performance, executive functioning, visuospatial ability
Tilvis et al. (2004)	Community	650	75,80,85¶	Longitudinal	Intermittent claudication	MMSE	NS
Johnston et al. (2004)	Community	4006	≥65	Longitudinal	Carotid stenosis/IMT	Modified MMSE, DST	General Cognitive function

Mathiesen et al. (2004)	Community	189/201	67.7/67.6‡	Cross-sectional	Carotid stenosis	WMS-R, SRT, Trial Making Tests A/B, PEG, WFT, WAIS	Attention, psychomotor speed, sustained attention, memory, and motor functioning
Vinkers et al. (2005)	Community	599	85-90	Longitudinal	Atherosclerosis	MMSE, Stroop, Digit-Coding Test, WLT	*No comparison with non-vascular controls*
Price et al. (2006)	Community	717	55-74	Cross-sectional	ABPI<0.9	WMS, RPM, VFT, Digit Symbol Test, NART	Psychomotor speed

*AH4=Alice Heim Reasoning Test; AVLT=Auditory Verbal Learning Task; BDCS=Behavioural Dyscontrol Scale; BVRT=Benton Visual Retention Test; CVLT=California Verbal Learning Test; CAMCOG=Cambridge Examination for Mental Disorders of the Elderly; CRT=Choice Reaction Test; CDRCAS=Cognitive Drug Research Computerised Assessment System; CANTAB=Computerised Tests from the Cambridge Neuropsychological Test Automated Battery; COWAT=Controlled Oral Word Association Test; CBTT=Corsi Block Tapping Test; GNT=Graded Naming Test; HDSR=Hasegawa's Dementia Scale; JOLT=Judgment of Line Orientation Test; MMSE=Mini-Mental State Examination; MCST=Modified Card Sorting Test; NART=National Adult Reading Test; PASAT=Paced Auditory Serial Addition Test; PALT=Paired Associates Learning Task; PEG=Pegboard Test; PMA=Primary Mental Abilities; RPM=Raven's Progressive Matrices; RMTFW=Recognition Memory Test for Faces and Words; RAVLT=Rey's Auditory Verbal Learning Test; RCF=Rey's Complex Figure; SRT=Seashore Rhythm Test; TBR=Test of Behavioural Rigidity; TMFE=Test of Mental Functions for the Elderly; TOL=Tower of London; TPD=Two-point Discrimination; VFT=Verbal Fluency Test; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale; WCST=Wisconsin Card Sorting Test; WFT=Word Fluency Test; WLT=Word Learning Test.

†Mean age of the total number of study subjects/cases. ‡Mean age of cases and controls, respectively.

APPENDIX B: The Edinburgh Artery Study design



APPENDIX C: Documentation relating to recruitment to follow-up cognitive function testing

C-1: Letter to general practitioners regarding subject's suitability to take part in cognitive function testing

To the Medical Centre/General Practice:

19th June 2002,

Dear Dr
Edinburgh Artery Study: Risks of cognitive impairment associated with vascular disease in the general population (EAS Cognitive Project – Follow-up Phase)

In 1998, the Edinburgh Artery Study conducted the first of two parts of a study examining the relationship between cardiovascular disease and cognitive function in men and women from the 11 general practices participating in the study. You and your colleagues very kindly allowed us to approach the Edinburgh Artery Study subjects registered at your practice and we then invited them to take part. We would now like to re-test these same people, so that we can relate changes in vascular status to changes in cognitive function over time.

As before, we intend to invite the participants to a clinic at the Medical School in Teviot Place, or if they prefer, we will visit them at home. We will be using the same tests to assess verbal skills, memory and logic. The tests which take about one hour to administer are: National Adult reading Test (NART), Raven's Standard Progressive Matrices and the Digit Symbol Substitution Test, the Logical Memory Test, a test of verbal fluency and the Hospital Anxiety Depression Scale. We would also like to include the Mini-Mental State Examination to assess cognitive ability and daily function.

We have enclosed a list of surviving participants from your practice who are, according to our records, still able to take part if they wish to do so. However, we would be very grateful if you could notify us of any patient who should not be approached by us to participate in this follow-up phase of the study. We have enclosed a form and a pre-paid envelope to assist you. If we have not heard from you within a month or so, we shall assume that we can go ahead and write to your patients on the list.

With many thanks,

Yours sincerely,

C-2: Letter to general practice manager regarding approval to invite subject to cognitive function testing

To the Practice Manager of:

3rd July 2002.

Dear Sir/Madam,

Edinburgh Artery Study: Risks of cognitive impairment associated with vascular disease in the general population (EAS Cognitive Project-Follow-up Phase)

The Edinburgh Artery Study began in 1988 and is a population-based cohort study of cardiovascular disease of 1592 men and women from the general population. The survey has been approved by the Lothian Health Research Ethics Committee. The study subjects were selected at random from 11 general practices spread throughout the city and were aged 55-74 years at baseline. In 1998, the Edinburgh Artery Study conducted the first of two parts of a study examining the relationship between cardiovascular disease and cognitive function and we would now like to re-test these same people so that we can relate changes in vascular status to changes in cognitive function over time.

However, several of the participants have now moved and changed general practitioner. According to our records, one of our study subjects is now registered at your practice, and I have enclosed his name and date of birth. I would be grateful if I may be given permission to approach this patient to invite him to take part. If so, it would be very helpful if you could notify us of any circumstances in which he should not be approached by us, for example, sight or hearing problems, previous strokes or dementia. I have enclosed a form and a pre-paid envelope to assist you.

To test their cognitive function, I intend to invite the participants to an interview at the Medical School in Teviot Place, or if they prefer, visit them at home. We shall be using the same tests as in 1998 to assess verbal skills, memory and logic. The tests which will take about one hour to administer are: National Adult Reading Test (NART), Raven's Standard Progressive Matrices and the Digit Symbol Substitution Test, the Logical Memory Test, a test of verbal fluency and the Hospital Anxiety Depression Scale. We would also like to include the Mini-Mental State Examination to assess cognitive function and daily function.

I shall be happy to answer any queries that you may have, and can be reached on (0131) XXX-XXXX. If we have not heard from you within a month or so, we shall assume that we can go ahead and write to the patient from your practice.

With many thanks,

Yours sincerely,

C-3: Subject's information sheet, letter of invitation and reply form

EDINBURGH ARTERY STUDY: Second Phase of the Cognitive Project

Subject Information Sheet

◆The purpose of this research:

Approximately four years ago, you took part in a series of tests which assessed memory, reasoning and verbal skills through written and spoken questions. This is called cognitive function testing. We are now interested in finding out how thinking skills change over time, and how they are influenced by changes in a person's arteries.

We would like to repeat these same tests on everyone who was tested four years ago. We would also like to include a new test that asks you to identify or do simple everyday activities. By comparing this with information we have already collected about your arteries, we can see if changes in arteries can influence thinking processes.

◆Arranging an appointment:

Your own general practitioner has been contacted again, so that we could explain about this second part of the project and to ensure that your doctor is happy for us to invite you to take part.

If you would like to participate, please return the reply slip, ticking the 'yes' box and including your current telephone number. We can either see you at the university or we can visit you at home, whatever is more convenient for you. We shall contact you by telephone at a later date to arrange an appointment. If you do not have a telephone, we will write to you with a provisional appointment. If you do not wish to take part, please tick 'no' and return the slip in the pre-paid envelope.

◆The appointment:

As before, the tests will last approximately <u>one hour</u>. We will begin by asking you a few short questions about your health and mood. We will then repeat the tests that you underwent the last time, including word pronunciation, memory, and reasoning. We will also include a new test that asks you simple questions about every day life. You are not obliged to complete any of the tests and you may withdraw at any point. The information we obtain is <u>completely confidential</u> and will only be used for data analysis in which study participants are identified by their study number. Data are not available to any person outside the research team, although you may wish us to notify your general practitioner if we come across anything of medical significance.

Mr/Mrs/Ms
Address:

1st July 2002

Dear Mr/Mrs/Ms

Many thanks for taking part in the Edinburgh Artery Study over the last several years. With your help, we have found out much useful information about the causes of heart attacks, strokes and diseases affecting the arteries of the legs. We have now completed the third and final clinic examination which took place at the Royal Infirmary of Edinburgh (or at your home) between 1999 and 2001. Although we have finished collecting data on your physical health, we would like to complete the study by carrying out a second series of the tests looking at your verbal skills, memory and thinking skills. This is known as cognitive function testing. You will already have undergone these tests with Dr or Mrs in 1998. We are now interested in seeing how you have changed over the last four years.

As before, there are the five tests of memory, word pronunciation and reasoning. We would also like to include another test that asks you to respond to simple questions. The series of tests will take approximately one hour and the information we obtain is completely confidential. We have enclosed an information sheet that gives you further details about these tests, and a reply slip and a pre-paid envelope. If you would like to take part, we can see you either at the university or, if you prefer, at your own home. Any travel expenses which you incur will be reimbursed by the Edinburgh Artery Study.

Reply slip:

If you would like to take part: Please tick 'yes' on the slip and also indicate whether you would like a university or home visit. Please return this in the pre-paid envelope. We will then contact you to arrange an appointment.

If you do not wish to take part: Please tick 'no' and return the slip in the envelope.

Please do not hesitate to contact me on 0131-XXX-XXXX if you have any questions about the tests or what is involved in the appointment. My address and telephone number are also shown at the top of the first sheet of this letter.

With many thanks,

Yours sincerely,

C-4: Reminding letter and map of University area

Mr/Mrs/Ms

9th January 2003

Dear Mr/Mrs/Ms

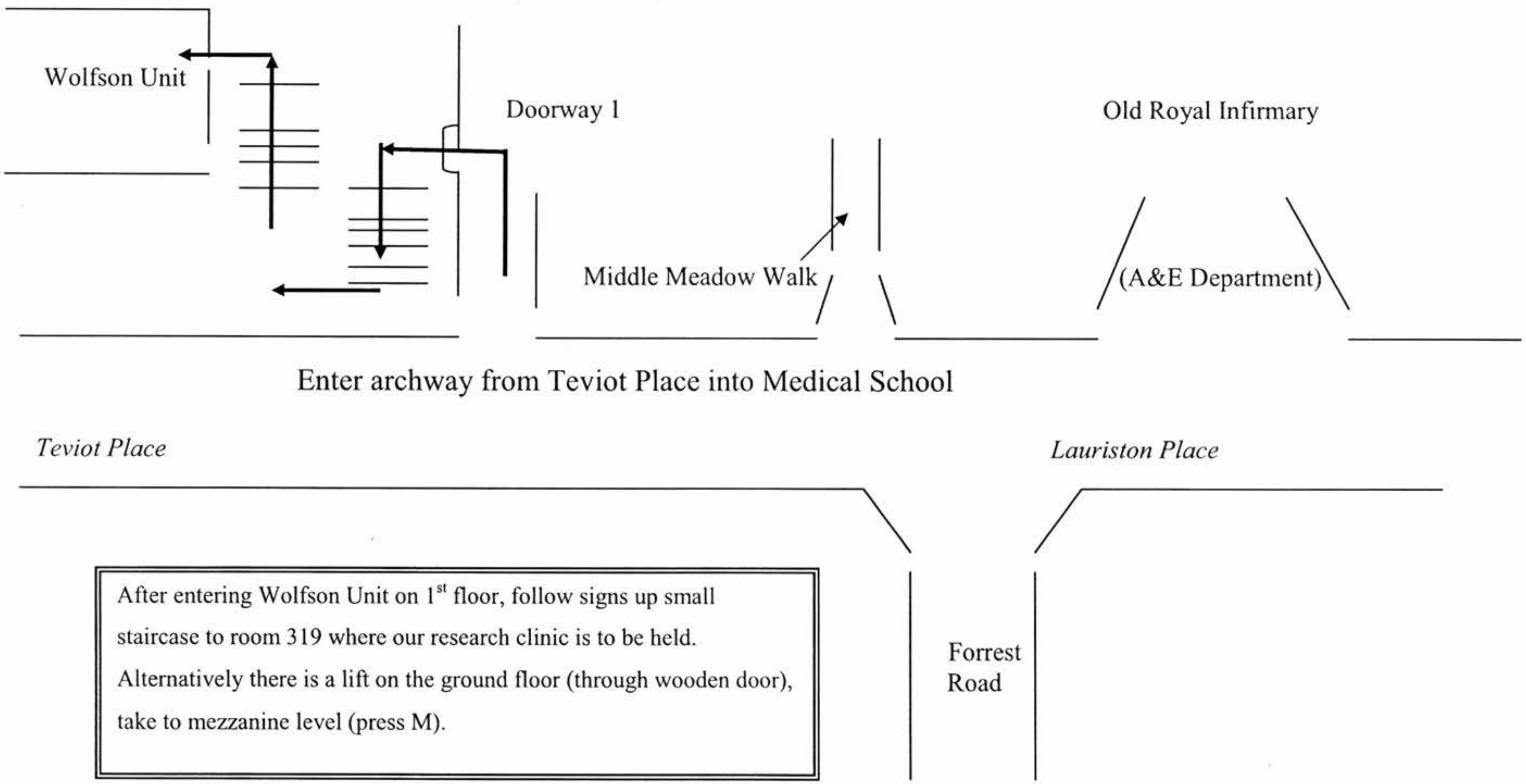
Thank you for agreeing to take part in the second part of the Edinburgh Artery Study Cognitive Project. I am writing to confirm that your appointment has been arranged for Tuesday 14th January at 2pm at the Medical School in Teviot Place and I have also enclosed a map to help you find your way to the room where the tests will take place. These tests take approximately one hour to complete but you may withdraw at any point during the interview if you so wish. I shall also be pleased to reimburse any travel expenses which you may incur.

If this appointment becomes unsuitable for any reason, please telephone me on XXX-XXXX to arrange an alternative time. I look forward to seeing you.

Yours sincerely,

MAP OF THE EDINBURGH UNIVERSITY MEDICAL SCHOOL – EAS COGNITIVE PROJECT

EDINBURGH UNIVERSITY MEDICAL SCHOOL



APPENDIX D: Cognitive function test battery

D-1: Consent form..

Study no…………..

EDINBURGH ARTERY STUDY: Second Phase of Cognitive Project

Consent Form

I have read the Subject Information Sheet and have had an opportunity to ask questions and discuss the study

I understand that I do not have to take part in this study and that a decision not to participate will not affect my standing with my general practitioner

I understand that I am free to withdraw from the tests at any time without having to give a reason

I understand that this is research from which I personally cannot expect to derive any direct benefit

I agree to participate in this study

Name (please print)	…………………………………………….
Signature	…………………………………………….
Signature of Investigator	…………………………………………….
Date	…………………………………………….

D-2: Medical Questionnaire

Patno..............

Do you have any of the following at present?	Yes	No
1. Difficulty reading because of poor vision?	☐	☐
2. Arthritis in your hands?	☐	☐
3. Hearing difficulties?	☐	☐
4. Parkinson's Disease?	☐	☐
5. A registered disability?......................................	☐	☐
Have you ever had:		
6. A stroke?	☐	☐
7. An injury that still affects your co-ordination?	☐	☐
8. An injury that still affects your thinking or memory?	☐	☐
9. Are you taking any medicines at present?	☐	☐

10. Is there anything else that you can think of which could get in the way of doing these tests?

....

D-3: Hospital Anxiety and Depression Scale

I feel tense or 'wound up'
Most of the time
A lot of the time
From time to time, occasionally
Not at all

I still enjoy the things I used to enjoy
Definitely as much
Not quite so much
Only a little
Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
Very definitely and quite badly
Yes, but not too badly
A little, but it doesn't worry me

I can laugh and see the funny side of things
As much as I always could
Not quite so much now
Definitely not so much now
Not at all

Worrying thoughts go through my mind
A great deal of the time
A lot of the time
From time to time but not too often
Only occasionally

I feel cheerful
Not at all
Not often
Sometimes
Most of the time

I can sit at ease and feel relaxed
Definitely
Usually
Not often
Not at all

I feel as if I am slowed down
Nearly all the time
Very often
Sometimes
Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach
Not at all
Ocasionally
Quite often
Very often

I have lost interest in my appearance
Definitely
I don't take so much care as I should
I may not take as much care
I take just as much care as ever

I feel restless as I have to be on the move
Very much indeed
Quite a lot
Not very much
Not at all

I look forward with enjoyment to things
As much as ever I did
Rather less than I used to
Definitely less than I used to
Hardly at all

I get sudden feelings of panic
Very often indeed
Quite often
Not very often
Not at all

I can enjoy a good book or radio or TV programme
Often
Sometimes
Not often
Very seldom

D-4: Mini-Mental State Examination

Patno ....
Date ....

Orientation-Time
Score one point for each correct answer

		Correct?	
1.	What day of the week is it?	Yes	No
	What date is it today?		
2.	Day	Yes	No
3.	Month	Yes	No
4.	Year	Yes	No
5.	What is the season?	Yes	No

(Allow flexibility when season changes)

Total correct.........................

Orientation-Place
Score one point for each correct answer

		Correct?	
	Can you tell me where we are now? For instance, what county or region we are in?	Yes	No
7.	What is the name of this town (city)?	Yes	No
8.	Which country are we in?	Yes	No
9.	What floor of the building are we on?	Yes	No
	What is the name of this place? (or: What is the address? If the subject is tested at home)	Yes	No

Total correct.........................

Memory-registration

I am going to name three objects. After I have finished saying all three, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

Name the following three objects taking one second to say each:
LEMON, KEY, BALL. Go!
Note items which are correct on the FIRST attempt and enter number correct under total.

	Correct?	
Lemon	Yes	No
Key	Yes	No
Ball	Yes	No

Total correct.........................

Attention and Calculation

12. Spell 'world' backwards

Correct?

D	Yes	No
L	Yes	No
R	Yes	No
O	Yes	No
W	Yes	No

Total correct.........................

Memory-Recall

Could you please tell me the three objects
I named earlier

Correct?

Lemon	Yes	No
Key	Yes	No
Ball	Yes	No

Total correct.........................

14. Could you please tell me what this is

Correct?

show WATCH	Yes	No
show PENCIL	Yes	No

Total correct.........................

15. I would like you to repeat the following
'No ifs, ands or buts'

Correct?

Yes No

Total correct.........................

Please read and obey the following:
Give the patient the paper with the printed sentence 'Close your eyes'
Ask the patient to read it and do what it says (only score when patient actually closes eyes)

Correct?

Yes No

Total correct.........................

Praxis-ideational

Read the following statement and then hand to the subject a sheet of paper. Make a point of handing to the subject's midline.

Please listen carefully to the instructions as I will explain it only once: I am going to give you a piece of paper. When I do, take the paper in your RIGHT hand. Fold the paper in half with both hands, and put the paper down in your lap.

Do not repeat instructions or coach. Score a move as correct only if it takes place in the correct sequence. Note each correct move and enter total number correct (Maximum score = 3 points).

	Correct?	
Right hand	Yes	No
Folds	Yes	No
On lap	Yes	No

Total correct.........................

Praxis-copying and drawing

	Correct?	
19. Copy this design (pattern)	Yes	No

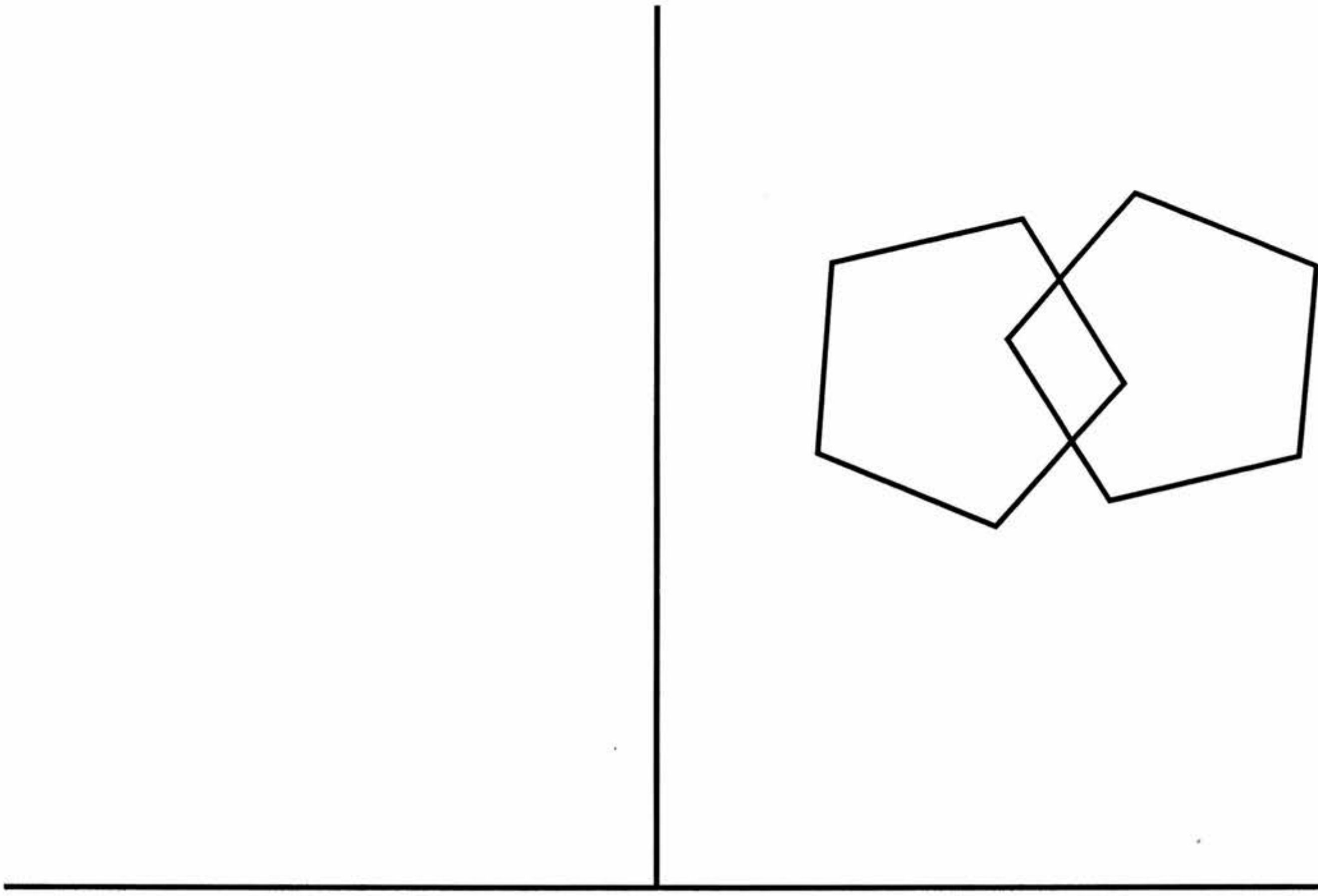
Total correct.........................

Praxis-Writing: Spontaneous

	Correct?	
Write a complete sentence in the space on the page indicated.	Yes	No

Total correct.........................

Overall total correct.............................



D-5: National Adult Reading Test

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DÉTENTE
EQUIVOCAL	IDYLL
NAÏVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

D-6: Logical Memory Test

LOGICAL MEMORY I: Score 1 point for each correct item (see Appendix A in Manual for Scoring Criteria)

STORY A

Anna/ Thompson/ of South/ Boston/ employed/ as a cook/in a school/ cafeteria/ reported/ at the City Hall/ Station/ that she had been held up/ on State Street/ the night before/ and robbed/ of fifty-six dollars/. She had four/ small children/ the rent was due/ and they had not eaten/ for two days/ The police/ touched by the woman's story/ took up a collection/ for her/

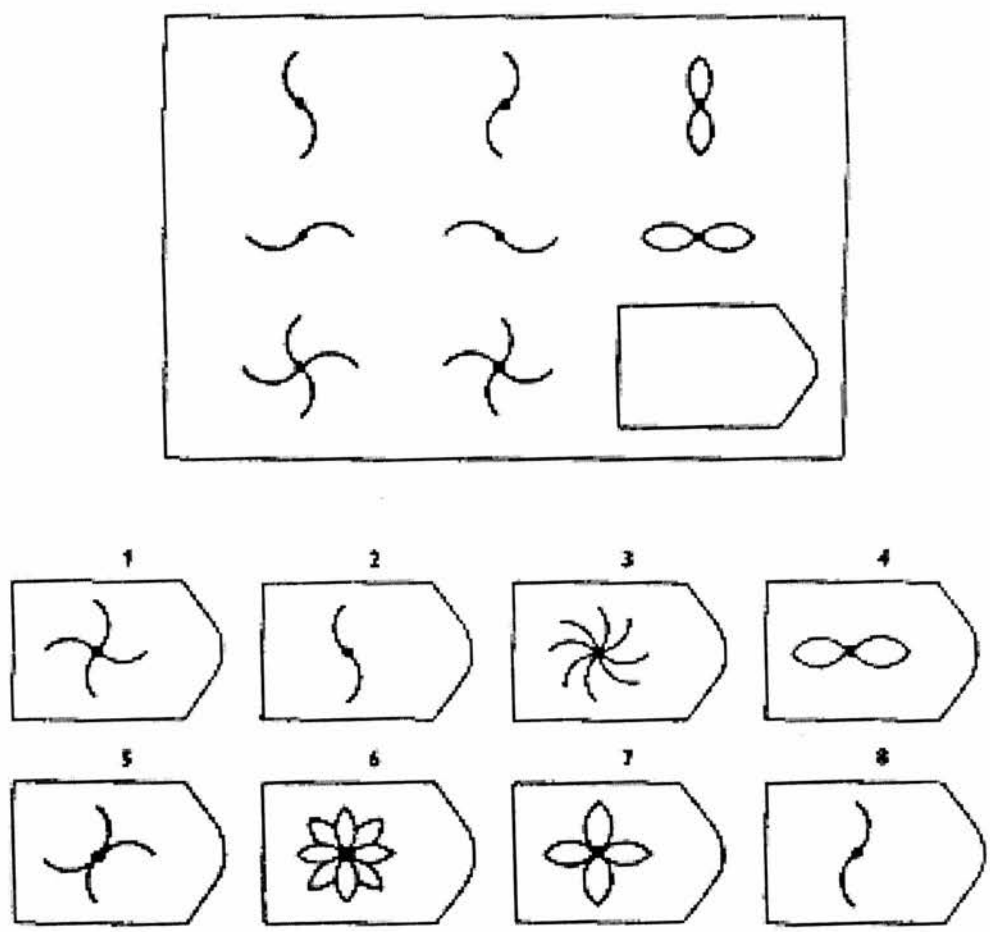
STORY B

Robert/ Miller/ was driving/ a ten-ton/ truck/ down a highway/ at night/ in the Mississippi/ Delta/ carrying eggs/ to Nashville/ when his axle/ broke/. His truck skidded/ off the road/ into a ditch/. He was thrown/ against the dashboard/ and was badly shaken/. There was no traffic/ and he doubted that help would come/. Just then his two-way radio/ buzzed/. He quickly answered/ "This is Grashopper/."

D-7: Raven's Standard Progressive Matrices

Sample Problem: E-1

E 1



D-8: Verbal Fluency Test

Patno..................

VERBAL FLUENCY

C	**F**	**L**

D-9: Digit Symbol-Coding Test

Patno.....................

1	2	3	4	5	6	7	8	9
—	⊥	⊐	L	⊔	O	∧	×	=

SCORE

SAMPLES

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4

1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3

6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7

9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

APPENDIX E: Baseline and follow-up criteria for fatal and non-fatal CVD

E-1: Angina pectoris

Baseline Examination Criteria

Three methods were applied in order to detect angina pectoris at the baseline clinical examination:

a. Subject's recall of a doctor's diagnosis of angina pectoris. Participants were asked if they had ever been told by a doctor that they had had angina.

b. WHO Questionnaire. Participants were enquired about whether they ever got pain or discomfort in the chest which met certain criteria with regard to site, onset, and duration.

c. Ischaemic changes on ECG. The ECG was coded according the Minnesota coding system and the following codes were used: 1.3.1-1.3.6; 4.1.1-4.1.2; 4.2-4.3; 5.1-5.3; and 7.1.1.

Five and 12-Year Follow-Up Examination Criteria

At the five-year examination, detection was based on the WHO questionnaire and ECG changes indicative of ischaemia. At the 12-year examination, only the WHO questionnaire was administered.

Criteria for new events during follow-up

A diagnosis of angina pectoris during the follow-up period was recorded if there was no WHO questionnaire evidence of angina at baseline, in addition to one of the following:

a. WHO evidence of angina during follow-up plus subject's recall of a doctor's diagnosis of angina,

OR

b. WHO evidence of angina during follow-up plus ischaemic changes on ECG,

OR

c. Clinical diagnosis of angina made by either a GP or at hospital.

E-2: Intermittent claudication

Baseline Examination Criteria

Presence of intermittent claudication at baseline was investigated with the use of the following procedures:

a. Subject's recall of a doctor's diagnosis of intermittent claudication. Subjects were asked if they had ever been told by a doctor that they had had hardening of the arteries in the leg.

b. WHO questionnaire on intermittent claudication. Participants were asked whether they ever experienced pain in either leg on walking which met specific criteria with regard to site, onset, and duration.

Five and 12-Year Follow-Up Examination Criteria

At baseline, intermittent claudication was assessed by using both subject's recall of a doctor's diagnosis and the WHO questionnaire. At five-year and 12-year examinations, subject's recall of a doctor's diagnosis of intermittent claudication had been replaced with a question (personal history) about whether participants had experienced pain at the back of either leg below the knee when walking.

Criteria for new events during follow-up

Intermittent claudication was diagnosed using the WHO angina and intermittent claudication questionnaire. Grade 1 was recorded if calf pain occurred when walking uphill or hurrying. Grade 2 was recorded if the pain also occurred while walking at ordinary pace on the level. 'Probable' intermittent claudication was defined as calf pain present on exercise but not at rest that otherwise did not fully meet the WHO questionnaire criteria.

E-3: Myocardial infarction

Baseline Examination Criteria

The detection of myocardial infarction at baseline was made on the basis of the following:

a. Subject's recall of a doctor's diagnosis of myocardial infarction. Participants were asked if they had ever been told by a doctor that they had had a heart attack (coronary thrombosis, myocardial infarction).

b. WHO Questionnaire. Subjects were asked whether they had ever experienced a severe pain across the front of the chest lasting for half an hour or more.

c. Diagnostic ECG. The following codes were used (Minnesota coding system): 1.1.1-1.1.2; 1.1.4; 1.2.1-1.2.2; 1.2.4-1.2.5; 1.2.7-1.3.0; and 9.2.

Five and 12-Year Follow-Up Examination Criteria

At five-year and 12-year examinations, identical to the baseline examination, the evaluation of myocardial infarction was made on the basis of the WHO questionnaire and diagnostic ECG codes. Instead of using subject's recall of a doctor's diagnosis, however, personal history was obtained by asking participants whether they had experienced for the first time a heart attack during the previous year.

Criteria for new events during follow-up

1. Non-fatal

   a. Definite myocardial infarction if two of the following three below were present:

i) Prolonged and lasting (>20 minutes) cardiac pain, anywhere in the anterior chest, left arm, or jaw (possibly also involving back, shoulder, right arm, or abdomen).

ii) The following diagnostic ECG codes (Minnesota coding system): 1.1.1-1.2.5; 1.2.7; or 9.2 plus 5.1 or 5.2.

iii) Elevated cardiac enzyme levels: creatine phosphokinase greater than twice the upper limits of normal, and one of the following also greater than twice the upper limits of normal: lactate dehydrogenase, glutamic oxalo-acetic transaminase, or the MB isoenzyme of creatine phosphokinase. The enzymes must have been measured within 72 hours of an acute event.

b. Possible myocardial infarction was coded if:

i) One of the above definite criteria was met plus either:

-equivocal ECG codes: 1.2.8-1.3.6; 4.1-4.3; 5.1-5.3; or 9.2.

-equivocal enzyme levels: above normal but not twice the normal or one was twice above the normal but could be attributed to another cause.

ii) Equivocal ECG codes and equivocal enzyme levels.

2. Fatal

a. Definite myocardial infarction was coded if one of the criteria below was met:

i) Post mortem evidence of acute myocardial infarction

ii) Definite criteria for myocardial infarction existed within four weeks prior to death.

iii) ICD-9 codes (International Classification of Disease) for cause of death were: 410-414 in addition to the participant having had a history of a definite or possible myocardial infarction; or 410-414 plus definite or possible criteria for myocardial infarction immediately preceding death; or 410-414 plus post mortem evidence of severe coronary atherosclerosis or previous myocardial infarction.

b. Possible myocardial infarction was recorded if:

-codes on death certificate were 410-414 without any other evidence of an acute event to be found.

3. Silent

Registered if the following Minnesota ECG codes were present: 1.1.1-1.2.5; 1.2.7; or 9.2 in addition to 5.1 or 5.2, in the absence of elevated levels of cardiac enzymes or cardiac pain, and normal ECG at baseline.

E-4: Stroke

Baseline Examination Criteria

At baseline, subject's recall of a doctor's diagnosis was used to enquire about history of stroke by asking participants whether they had ever been told by a doctor that they had had one.

Five and 12-Year Follow-Up Examination Criteria

As above, subject's recall of a doctor's diagnosis used at baseline had been replaced with personal history at five-year and 12-year examinations, enquiring participants about whether they had experienced a stroke for the first time in the year before the examination.

Criteria for new events during follow-up

1. Non-fatal

   a. Definite stroke was recorded if one of the following criteria was present:

      i) A history of onset of symptoms of less than 48 hours, plus clinical confirmation of a focal or global disturbance of cerebral function lasting for more than 24 hours.

      ii) Computerised tomography (CT) scan showed evidence of cerebral infarction or haemorrhage.

   b. Possible stroke was coded if:

      -primary or secondary discharge diagnosis included ICD-9 codes of 431, 432, 434, 436 or 437.

2. Fatal

a. Definite stroke was recorded if one of the following was present:

i) Post mortem evidence of cerebral infarction or haemorrhage.

ii) Criteria for definite stroke were met within the six weeks prior to death.

b. Possible stroke was coded if:

-death certificate codes of underlying or immediate cause of death were ICD9 431-437, without any other evidence available.

APPENDIX F: Number of subjects meeting individual confirmatory criteria for CVD at baseline and follow-up

F-1: Angina pectoris

Confirmatory criteria	N	%
Baseline Examination		
Positive WHO Questionnaire AND recall of a doctor's diagnosis of angina	19	16.8
OR		
Positive WHO Questionnaire AND ECG evidence of ischaemia	11	9.7
Five and 12-year Follow-up Examination		
~Positive WHO Questionnaire AND ECG evidence of ischaemia (5-year examination)	14	12.4
~Positive WHO Questionnaire (12-year examination)	23	20.4
Follow-up		
No WHO evidence at baseline *plus either*:		
i) Positive WHO Questionnaire AND recall of a doctor's diagnosis of angina	25	22.1
OR		
ii) Positive WHO Questionnaire AND ECG evidence of ischaemia	5	4.4
OR		
ii) Clinical diagnosis of angina investigated by a GP or a hospital	16	14.1
Total	113	100.0

F-2: Intermittent claudication

Confirmatory criteria	N	%
Baseline Examination		
Recall of a doctor's diagnosis of intermittent claudication	0	0.0
<u>OR</u>		
Positive WHO Questionnaire:		
~Grade 1	2	3.2
~Grade 2	5	8.1
~Probable	0	0.0
Five and 12-year Follow-up Examination		
Recall of a doctor's diagnosis of intermittent claudication	0	0.0
<u>OR</u>		
Positive WHO Questionnaire:		
~Grade 1	9	14.6
~Grade 2	4	6.4
~Probable	16	25.9
Follow-up		
Positive WHO Questionnaire:		
~Grade 1	4	6.4
~Grade 2	4	6.4
~Probable	18	29.0
Total	62	100.0

F-3: Myocardial infarction

Confirmatory criteria	N	%
Baseline Examination		
Positive WHO Questionnaire AND recall of a doctor's diagnosis of MI	4	7.5
OR		
Positive WHO Questionnaire AND ECG evidence of previous MI	1	1.9
OR		
Recall of a doctor's diagnosis of MI AND ECG evidence of previous MI	6	11.3
Five and 12-year Follow-up Examinations		
Positive WHO Questionnaire AND ECG evidence of previous MI	8	15.1
Follow-up		
Definite MI		
Chest pain (for at least 20 minutes) AND ECG evidence of previous MI	2	3.8
OR		
Chest pain (for at least 20 minutes) AND elevated enzyme levels	19	35.8
OR		
ECG evidence of previous MI AND elevated enzyme levels	0	0.0
Possible MI One of the above definite criteria *plus* either:		
i) Equivocal ECG codes	4	7.5
OR		
Equivocal enzyme levels	3	5.7
OR		
ii) Equivocal ECG AND enzyme levels	1	1.9
Silent MI ECG evidence of MI *in the absence* of elevated enzymes and chest pain	5	9.4
Total	53	100.0

F-4: Stroke

Confirmatory criteria	N	%
Baseline Examination		
Recall of a doctor's diagnosis of stroke	6	30.0
Five and 12-year Examinations		
Recall of a doctor's diagnosis of stroke	3	15.0
Follow-up		
Definite stroke		
Clinical criteria (onset of symptoms <48 hours with duration of >24 hours)	4	20.0
OR		
Computerised tomography (positive results)	5	25.0
Possible stroke		
Hospital discharge diagnosis	2	10.0
Total	20	100.0